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| (54) Title: HUMAN BREAST AND OVARIAN CANCER ASSOCIATED GENE SEQUENCES AND POLYPEPTIDES (57) Abstract This invention relates to newly identified breast, ovarian, breast cancer and/or ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens", and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, particularly disorders of the breast and/or ovary, including the presence of breast cancer and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, particularly disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention. | | |

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Human Breast and Ovarian Cancer Associated Gene Sequences and Polypeptides

5 *Field of the Invention*

This invention relates to newly identified breast, ovarian, breast cancer, and ovarian cancer related polynucleotides and the polypeptides encoded by these polynucleotides herein collectively known as "breast/ovarian cancer antigens," and to the complete gene sequences associated therewith and to the expression products thereof, as well as the use of such
10 breast/ovarian cancer antigens for detection, prevention and treatment of disorders of the female reproductive system, specifically disorders of the breast or ovary, particularly the presence of breast and/or ovarian cancer. This invention relates to the breast/ovarian cancer antigens as well as vectors, host cells, antibodies directed to breast/ovarian cancer antigens and recombinant and synthetic methods for producing the same. Also provided are
15 diagnostic methods for diagnosing and treating, preventing and/or prognosing disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention. The present invention further
20 relates to methods and/or compositions for inhibiting the production and/or function of the polypeptides of the present invention.

Background of the Invention

Breast cancer represents the most frequent cause of early morbidity and mortality in
25 women in North America (Harris et al, New Eng. J. Med. 327:319, 390 and 473 (1992)). It is generally believed that this malignancy arises from a multi step process involving mutations in a relatively small number of genes, perhaps 10 or less. These mutations result in significant changes in the growth and differentiation of breast tissue that allow it to grow independent of normal cellular controls, to metastasize, and to escape immune surveillance. The genetic
30 heterogeneity of most breast cancers suggests that they arise by a variety of initiating events

and that the characteristics of individual cancers are due to the collective pattern of genetic changes that accumulate (Harris et al. *New Eng. J. Med.* 327:319, 390 and 473 (1992)).

The classes of genes that are involved in breast cancer are not unlike those found in a number of other well characterized malignancies, although some are highly specific for breast cancer. In particular, mutations in the genes that encode receptors involved in binding to estrogen and progesterone are particularly important because they likely cause the breast cells to proliferate while rendering them unresponsive to the antitumor effects of these hormones in advanced malignancy. In addition, changes in the genes that encode growth factors, other receptors, signal transduction molecules, and transcription factor molecules are frequently involved and have alterations that are involved in the development and progression of breast cancer (King, *Nature Genetics* 2:125 (1992)). The characterization of the type and number of mutations seen in individual breast cancers is useful in classifying the biological properties of individual cancers and in determining the prognosis for individual patients. For example, the *erbB2/HER2/neu* gene is particularly valuable in predicting the prognosis of both node-positive and node-negative patients based on the amplification status of the gene (King, *Science* 250:1684 (1990)). Several additional members of this family have been discovered but the ligand for *erbB2/HER2/neu* remains unknown. It is anticipated that further advances in therapeutics will be achieved by the development of therapies that disrupt aberrant growth signaling pathways or affect the cellular interactions of breast cancer cells with native stroma or metastatic sites.

Although oncogenes are likely to be very important in breast cancer, tumor suppressor genes may also play an important role. Certain of these genes, including *p53* and *Rb-1*, are essential to the normal mechanisms that control cell cycle events, especially those checkpoints at the border of the different stages of the cell cycle (Hollstein et al, *Science* 253:49 (1991); Srivastava et al, *Nature* 348:747 (1990)).

In 1969, Li and Fraumeni documented a familial cancer syndrome that had an autosomal dominant pattern of expression (Li et al, *Ann. Intern. Med.* 71:747 (1969)). Members of these families had sarcomas, breast cancers, brain tumors, leukemias, adrenocortical carcinomas, and other malignancies. Family studies demonstrated that the gene responsible for the syndrome was located on chromosome 17, and examination of the *p53* gene as a candidate gene revealed that this gene was mutated in five families (Malsin et al, *Science* 250:1233 (1990)). In the last two years, two genes linked to familial breast cancer,

designated BRCA1 and BRCA2, have been isolated and characterized. BRCA1 is at 17q21 (Claus et al, Am. J. Epidemiology 131:961 (1990); Hall et al, Science 250:1684 (1990); Easton et al, Am. J. of Human Genetics 52 (4):678 (1993); Black et al, Am. J. of Human Genetics 52 (4):702 (1993); Bowcock et al, Am. J. of Human Genetics 52 (4):718 (1993); Miki et al, Science 266:66 (1995)). The demonstration of loss of heterozygosity (LOH) at 17q25 has defined another potential tumor suppressor gene (Lindblom et al, Human Genetics 91:6 (1993); Cornelis et al, Oncogene 8:781 (1993); Theile et al, Oncogene 10:439 (1995)).

There is a need, therefore, for identification and characterization of such factors that modulate activation and differentiation of breast and ovarian cells, both normally and in disease states. In particular, there is a need to isolate and characterize additional molecules that mediate apoptosis, DNA repair, tumor-mediated angiogenesis, genetic imprinting, immune responses to tumors and tumor antigens and, among other things, that can play a role in detecting, preventing, ameliorating or correcting dysfunctions or diseases.

The present invention relates at least in part, to a novel breast and ovarian and breast and ovarian cancer related polynucleotides and polypeptides. The discovery of these breast and ovarian cancer related polynucleotides provides new compositions which are useful in the diagnosis, prevention and treatment of disorders of the female reproductive system, particularly of the ovary including, but not limited to ovarian cancer, and the breast, including but not limited to breast cancer.

Summary of the Invention

The present invention includes isolated nucleic acid molecules comprising, or alternatively, consisting of, a breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotide sequence disclosed in the sequence listing (as SEQ ID Nos:1 to 418) and/or contained in a human cDNA clone described in Tables 1, 2 and 5 and deposited with the American Type Culture Collection ("ATCC"). Fragments, variant, and derivatives of these nucleic acid molecules are also encompassed by the invention. The present invention also includes isolated nucleic acid molecules comprising, or alternatively consisting of, a polynucleotide encoding a breast, ovarian, breast cancer, and/or ovarian cancer polypeptide. The present invention further includes breast, ovarian, breast cancer, and/or ovarian cancer polypeptides encoded by these polynucleotides. Further provided for are amino acid

sequences comprising, or alternatively consisting of, breast, ovarian, breast cancer, and/or ovarian cancer polypeptides as disclosed in the sequence listing (as SEQ ID Nos: 419 to 836) and/or encoded by a human cDNA clone described in Tables 1, 2 and 5 and deposited with the ATCC. Antibodies that bind these polypeptides are also encompassed by the invention.

5 Polypeptide fragments, variants, and derivatives of these amino acid sequences are also encompassed by the invention, as are polynucleotides encoding these polypeptides and antibodies that bind these polypeptides. Also provided are diagnostic methods for diagnosing and treating, preventing, and/or prognosing disorders related to the female reproductive system, specifically disorders related to the breast and/or ovary, including breast cancer
10 and/or ovarian cancer, and therapeutic methods for treating such disorders. The invention further relates to screening methods for identifying agonists and antagonists of breast/ovarian cancer antigens of the invention.

Detailed Description

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Tables

Table 1 summarizes some of the breast/ovarian cancer antigens encompassed by the invention (including contig sequences (SEQ ID NO:X) and the cDNA clone related to the contig sequence) and further summarizes certain characteristics of the breast/ovarian cancer
20 polynucleotides and the polypeptides encoded thereby. The first column shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention. The second column provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column, "Gene Name," and the fourth column, "Overlap," provide a putative identification
25 of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database and the database accession no. for the database sequence having similarity, respectively. The fifth and sixth columns provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as
30 SEQ ID NO:Y. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity), respectively, observed between the aligned sequence

segments of the translation product of SEQ ID NO:X and the database sequence. The ninth column provides a unique "Clone ID" for a cDNA clone related to each contig sequence.

Table 2 summarizes ATCC Deposits, Deposit dates, and ATCC designation numbers of deposits made with the ATCC in connection with the present application.

5 Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, fifteen or more of any one or more of these public EST sequences are optionally excluded from certain embodiments of the invention.

Table 4 lists residues comprising antigenic epitopes of antigenic epitope-bearing fragments present in most of the breast, ovarian, breast cancer or ovarian cancer associated
10 polynucleotides described in Table 1 as predicted by the inventors using the algorithm of Jameson and Wolf, (1988) Comp. Appl. Biosci. 4:181-186. The Jameson-Wolf antigenic analysis was performed using the computer program PROTEAN (Version 3.11 for the Power MacIntosh, DNASTAR, Inc., 1228 South Park Street Madison, WI). Breast, ovarian, breast cancer and/or ovarian cancer associated polypeptides (e.g., SEQ ID NO:Y, polypeptides
15 encoded by SEQ ID NO:X, or polypeptides encoded by the cDNA in the referenced cDNA clone) may possess one or more antigenic epitopes comprising residues described in Table 4. It will be appreciated that depending on the analytical criteria used to predict antigenic determinants, the exact address of the determinant may vary slightly. The residues and locations shown in column two of Table 4 correspond to the amino acid sequences for most
20 breast, ovarian, breast cancer and/or ovarian cancer associated polypeptide sequence shown in the Sequence Listing.

Table 5 shows the cDNA libraries sequenced, and ATCC designation numbers and vector information relating to these cDNA libraries.

25

Definitions

The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

30 In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be

"isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X (as described in column 1 of Table 1) or the related cDNA clone (as described in column 9 of Table 1 and contained within a library deposited with the ATCC). For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having an amino acid sequence encoded by a polynucleotide of the invention as broadly defined (obviously excluding poly-Phenylalanine or poly-Lysine peptide sequences which result from translation of a polyA tail of a sequence corresponding to a cDNA).

In the present invention, "SEQ ID NO:X" was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X is deposited at Human Genome Sciences, Inc. (HGS) in a catalogued and archived library. As shown in column 9 of Table 1, each clone is identified by a cDNA Clone ID. Each Clone ID is unique to an individual clone and the Clone ID is all the information needed to retrieve a given clone from the HGS library. In addition to the individual cDNA clone deposits, most of the cDNA libraries from which the clones were derived were deposited at the American Type Culture Collection (hereinafter "ATCC"). Table 5 provides a list of the deposited cDNA libraries. One can use the Clone ID to determine the library source by reference to Tables 2 and 5. Table 5 lists the deposited cDNA libraries by name and links each library to an ATCC Deposit. Library names contain four characters, for example, "HTWE." The name of a cDNA clone ("Clone ID") isolated from that library begins with the same four characters, for example "HTWEP07". As mentioned below, Table 1 correlates the Clone ID names with SEQ ID NOs. Thus, starting with a SEQ ID NO, one can use Tables 1, 2 and 5 to determine the corresponding Clone ID, from which library it came and in which ATCC deposit the library is contained. Furthermore,

it is possible to retrieve a given cDNA clone from the source library by techniques known in the art and described elsewhere herein. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposits were made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for the purposes of patent procedure.

A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, or the complement thereof (e.g., the complement of any one, two, three, four, or more of the polynucleotide fragments described herein), and/or sequences contained in the related cDNA clone within a library deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC (750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

Also included within "polynucleotides" of the present invention are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M NaH₂PO₄; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100 ug/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

The polynucleotides of the present invention can be composed of any polyribonucleotide or polydeoxribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15 kb, 10 kb, 7.5kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

"SEQ ID NO:X" refers to a breast/ovarian cancer antigen polynucleotide sequence described in Table 1. SEQ ID NO:X is identified by an integer specified in column 1 of Table 1. The polypeptide sequence SEQ ID NO:Y is a translated open reading frame (ORF)

encoded by polynucleotide SEQ ID NO:X. There are 418 breast/ovarian cancer antigen polynucleotide sequences described in Table 1 and shown in the sequence listing (SEQ ID NO:1 through SEQ ID NO:418). Likewise there are 418 polypeptide sequences shown in the sequence listing, one polypeptide sequence for each of the polynucleotide sequences (SEQ ID NO:419 through SEQ ID NO:836). The polynucleotide sequences are shown in the sequence listing immediately followed by all of the polypeptide sequences. Thus, a polypeptide sequence corresponding to polynucleotide sequence SEQ ID NO:1 is the first polypeptide sequence shown in the sequence listing. The second polypeptide sequence corresponds to the polynucleotide sequence shown as SEQ ID NO:2, and so on. In otherwords, since there are 418 polynucleotide sequences, for any polynucleotide sequence SEQ ID NO:X, a corresponding polypeptide SEQ ID NO:Y can be determined by the formula $X + 418 = Y$. In addition, any of the unique "Sequence/Contig ID" defined in column 2 of Table 1, can be linked to the corresponding polypeptide SEQ ID NO:Y by reference to Table 4.

The polypeptides of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation,

hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

The breast, ovarian, breast cancer and/or ovarian cancer polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the polypeptides of the present invention in methods which are well known in the art.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to

a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

"A polypeptide having functional activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular assay, such as, for example, a biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention).

The functional activity of the breast/ovarian cancer antigen polypeptides, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the present invention for binding to an antibody to the full length polypeptide antibody, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

In another embodiment, where a ligand is identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See

generally, Phizicky, E., et al., Microbiol. Rev. 59:94-123 (1995). In another embodiment, physiological correlates polypeptide of the present invention binding to its substrates (signal transduction) can be assayed.

In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the present invention and fragments, variants derivatives and analogs thereof to elicit polypeptide related biological activity (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

Breast, Ovarian, Breast Cancer and Ovarian Cancer Associated Polynucleotides and Polypeptides of the Invention

It has been discovered herein that the polynucleotides described in Table 1 are expressed at significantly enhanced levels in human breast, ovarian, breast cancer and/or ovarian cancer tissues. Accordingly, such polynucleotides, polypeptides encoded by such polynucleotides, and antibodies specific for such polypeptides find use in the prediction, diagnosis, prevention and treatment of disorders related to the female reproductive system, specifically disorders of the breast and/or ovary, including breast cancer and/or ovarian cancer as more fully described below.

Table 1 summarizes some of the polynucleotides encompassed by the invention (including contig sequences (SEQ ID NO:X) and the related cDNA clones) and further summarizes certain characteristics of these breast, ovarian, breast cancer and/or ovarian cancer associated polynucleotides and the polypeptides encoded thereby.

Table 1

| Seq ID No. | Sequence/Contig ID | Gene Name | Overlap | HGS Nucleotide Start End | % Identity | % Similarity | Clone ID |
|------------|--------------------|---|------------|-----------------------------|------------|--------------|----------|
| 1 | 419266 | monoamine oxidase B [Homo sapiens] >gi 187376 monamine oxidase B [Homo sapiens] >bbs 134021 monoamine oxidase B, MAO B [human, platelet, Peptide Partial, 520 aa] [Homo sapiens] >pir JH0817 JH0817 amine oxidase (flavin-containing) (EC 1.4.3.4) B - human > | gi 187359 | 2 1021 | 95 | 95 | HAGFP75 |
| 2 | 429114 | | | 51 383 | | | HATDC43 |
| 3 | 506777 | | | 51 233 | | | HRGCY74 |
| 4 | 508678 | (AF059293) cytokine-like factor-1 precursor [Homo sapiens] >sp O75462 O75462 CYTOKINE-LIKE FACTOR-1 PRECURSOR. Length = 422 DNA helicase [Homo sapiens] >pir A58836 A55311 DNA helicase RECQL - human Length = 659 | gi 3372627 | 3 155 | 100 | 100 | HFJUG81 |
| 5 | 508968 | | gi 619863 | 2 739 | 95 | 96 | HHTLH91 |
| 6 | 509029 | | 770 1096 | | | | HLMDG72 |
| 7 | 519726 | | 359 529 | | | | HCSSB83 |

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|----|--------|--|---------------------|------|------|-------|---------|
| 8 | 522632 | | | 3 | 299 | | HRGBG45 |
| 9 | 524655 | | | 522 | 686 | | HJSGS36 |
| 10 | 525847 | glyoxalase II [Homo sapiens] >sp Q16775 GLO2_HUMAN HYDROXYACYLGLUTATHIONE HYDROLASE (EC 3.1.2.6) (GLYOXALASE II) (GLX II). Length = 260 | gnl PID e1971 27 | 1 | 162 | 54 73 | H5EDP14 |
| 11 | 530306 | | | 239 | 355 | | HCHCC28 |
| 12 | 532818 | (AF035178) elongation factor 1 A2 [Oryctolagus cuniculus] >gi 38456 elongation factor 1 alpha-2 [Homo sapiens] >pir S35033 EFHUA2 translation elongation factor eEF-1 alpha-2 chain - human >sp Q05639 EF12_HUMAN ELONGATION FACTOR 1-ALPHA 2 (EF-1-ALPHA-2) (S | gi 3098311 | 43 | 441 | 95 95 | HAMFD92 |
| 13 | 533385 | | | 1258 | 1827 | | HTWAO42 |
| 14 | 533532 | actin capping protein alpha subunit [Homo sapiens] >gi 2393732 (AC002543) f-actin capping protein alpha-2 subunit [Homo sapiens] >sp P47755 CAZ2_HUMAN F- ACTIN CAPPING PROTEIN ALPHA-2 SUBUNIT (CAPZ). >gi 433308 capping protein alpha [Homo sapiens] {SUB 3-2 | gi 595255 | 18 | 947 | 95 95 | HETCD42 |

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|----|--------|---|-----|------|-----|-----|---------|
| 15 | 534852 | (AF041472) ataxin-2 [Mus musculus] >sp O70305 O70305 SPINOCEREBELLAR ATAXIA 2 HOMOLOG (ATAXIN-2). Length = 1285 R kappa B [Homo sapiens] >pir S52863 S52863 DNA-binding protein R kappa B - human >sp Q15312 Q15312 R KAPPA B. Length = 1324 | 3 | 869 | 77 | 77 | HCE4Q55 |
| 16 | 537910 | | 3 | 443 | 100 | 100 | H1OAO52 |
| 17 | 538460 | | 574 | 1026 | | | HSSMY42 |
| 18 | 539577 | transcriptional activator [Homo sapiens] >gnl PID d1005685 hSNF2b [Homo sapiens] >pir S45252 S45252 SNF2beta protein - human >gi 4056413 (AC006127) SN24_HUMAN; nuclear protein GRB1; homeotic gene regulator; SNF2-BETA [Homo sapiens] {SUB 814-1474} Length = | 1 | 540 | 89 | 89 | HKADQ93 |
| 19 | 548379 | complement protein C7 precursor [Homo sapiens] >pir A27340 A27340 complement C7 precursor - human >sp P10643 CO7_HUMAN COMPLEMENT COMPONENT C7 PRECURSOR. Length = 843 proteasome subunit HsN3 [Homo sapiens] >pir S50147 S50147 multicatalytic endopeptidase complex (EC 3.4.99.46) beta chain N3 - human >sp P28070 PRCB_HUMAN PROTEASOME BETA CHAIN PRECURSOR (EC 3.4.99.46) (MACROPAIN BETA CHAIN) | 92 | 1336 | 92 | 92 | HATCK25 |
| 20 | 548489 | | 3 | 857 | 99 | 99 | HCGAF33 |

(MULTICATALYTIC ENDOPEPTIDASE
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|----|--------|---|------------|-----|------|-----|-----|-----|---------|
| 21 | 548595 | inosine monophosphate dehydrogenase type II [Homo sapiens] >gi 1702964 inosine monophosphate dehydrogenase type II [Homo sapiens] >pir 52303 A31997 IMP dehydrogenase (EC 1.1.1.205) II - human >sp P12268 IMD2_HUMAN INOSINE-5'-MONOPHOSPHATE DEHYDROGENASE | gi 602458 | 971 | 1525 | 100 | 100 | 100 | HTXEE92 |
| 22 | 549337 | stromelysin-3 precursor [Homo sapiens] Length = 488 | gi 456257 | 449 | 1081 | 96 | 96 | 96 | HJMAF23 |
| 23 | 549777 | | | 54 | 293 | | | | HPMAC61 |
| 24 | 553091 | pancreatic peptidylglycine alpha-amidating monooxygenase, PAM=membrane-bound isoform {alternatively spliced, clone PAM-3, transmembrane domain (Ba region)} [human, islet cell tumor cell line QGP-1, Peptide Partial, 971 aa] [Homo sapiens] >sp Q16252 Q16252 | bbs 159681 | 898 | 2598 | 97 | 97 | 97 | HEMFU73 |
| 25 | 553827 | B-CAM gene product [Homo sapiens] >pir 37202 37202 B-CAM protein - human Length = 588 | gi 535179 | 2 | 388 | 80 | 80 | 80 | HBHMI67 |

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|----|--------|---|-------------|-----|------|-----|-----|---------|---------|
| 26 | 556350 | | | 263 | 655 | | | | HCHOC59 |
| 27 | 556351 | 'FKBP52; 52 kD FK506 binding protein' [Homo sapiens] >pir A46372 A46372 immunophilin FKBP52 - human >sp Q02790 FKB4_HUMAN P59 PROTEIN (HSP BINDING IMMUNOPHILIN) (HBI) (POSSIBLE PEPTIDYL-PROLYL CIS-TRANS ISOMERASE) (EC 5.2.1.8) (PPIASE) (ROTAMASE) (FKBP5 ubiquitin conjugating enzyme [Homo sapiens] >pir A49630 A49630 ubiquitin conjugating enzyme - human (fragment) Length = 298 (AD001530) putative [Homo sapiens] >sp G2335055 G2335055 XAP-5. >gnl PID d1012538 HXC-26 [Homo sapiens] {SUB 15-339} >gil 203974 XAP-5 gene product [Homo sapiens] {SUB 66-339} Length = 339 adipocyte lipid-binding protein [Homo sapiens] >pir A33363 FZHU fatty acid-binding protein, adipocyte - human >sp P15090 FABA_HUMAN FATTY ACID-BINDING PROTEIN, ADIPOCYTE (AFABP) (ADIPOCYTE LIPID-BINDING PROTEIN) (ALBP) (A-FABP). {SUB 2-132} Length = 132 N-cadherin [Homo sapiens] Length = 747 | gil 186390 | 2 | 1216 | 97 | 97 | HE8DF57 | |
| 28 | 557007 | | gil 388309 | 3 | 698 | 99 | 100 | | HTEJK85 |
| 29 | 558140 | | gil 2335055 | 3 | 1070 | 71 | 71 | | HKAAM18 |
| 30 | 558456 | | gil 178347 | 69 | 332 | 100 | 100 | | HISBQ67 |
| 31 | 558708 | | gil 416293 | 3 | 515 | 79 | 79 | | HSYBX61 |
| 32 | 574789 | | | 301 | 402 | | | | HLDNM79 |

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|----|--------|---|------------|----|-----|-----|-----|-----------|
| 33 | 578203 | | | 2 | 445 | | | H6EDN57 |
| 34 | 585385 | precursor polypeptide (AA -21 to 782) [Homo sapiens] >pir A35954 A35954 endoplasmin precursor - human >sp P14625 ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803 leukocyte adhesion glycoprotein precursor [Homo sapiens] Length = 1152 | gij37261 | 99 | 347 | 71 | 71 | 110FMPT70 |
| 35 | 588869 | | gij307114 | 1 | 720 | 98 | 98 | HDPEK39 |
| 36 | 597076 | preferentially expressed antigen of melanoma [Homo sapiens] >sp P78395 P78395 PREFERENTIALLY EXPRESSED ANTIGEN OF MELANOMA. Length = 509 sigma receptor [Homo sapiens] >gij1916800 SR31747 binding protein 1 [Homo sapiens] >gij2914740 (AF001977) type I sigma receptor [Homo sapiens] >pir JC5266 JC5266 sigma receptor 1 - human >sp Q99720 Q99720 SIGMA RECEPTOR. Length = 223 | gij1903384 | 80 | 811 | 77 | 77 | HEHE66 |
| 37 | 598656 | | gij1783387 | 3 | 587 | 100 | 100 | HM.EIY05 |

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|----|--------|---|-----------------|-----|------|-----|-----|----------|
| 38 | 611880 | Acetyl-CoA:acetyltransferase (EC 2.3.1.9) (Acetoacetyl-CoA thiolase), [Escherichia coli] >gi 1788554 (AE000311) acetyl-CoA acetyltransferase [Escherichia coli] >pir F64992 F64992 hypothetical protein b2224 - Escherichia coli (strain K-12) >sp P76461 ATOB_ | gn PID d1016745 | 1 | 108 | 100 | 100 | HOVAS88 |
| 39 | 614329 | ORF, HEIR-1; pot. neuroblastoma-associated regulator [Homo sapiens] >gi 395338 helix-loop-helix protein [Homo sapiens] >gi 512437 HEIR-1 [Homo sapiens] {SUB 30-148} Length = 148 | gi 490013 | 300 | 755 | 86 | 86 | HIFPCQ02 |
| 40 | 616066 | | | 121 | 213 | | | HSIGC05 |
| 41 | 620956 | ribosomal protein S9 [Rattus norvegicus] >pir JN0587 S21497 ribosomal protein S9 - rat Length = 194 | gi 57143 | 3 | 473 | 95 | 97 | HOFOB28 |
| 42 | 621889 | unnamed protein product [unidentified] >gi 468550 CCT (chaperonin containing TCP-1) epsilon subunit [Mus musculus] >pir S43061 S43061 t-complex-type molecular chaperone Ccte - mouse Length = 541 | gn PID c306129 | 16 | 423 | 95 | 97 | HOFOC44 |
| 43 | 624017 | (AB003732) polyubiquitin [Cricetulus griseus] >sp O35080 O35080 POLYUBIQUITIN. >gi 4105408 (AF045474) polyubiquitin [Schistosoma mansoni] {SUB 694-988} Length = 1038 | gi 2627133 | 1 | 1170 | 95 | 97 | HMCBS12 |

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|----|--------|--|-----------------------|----|------|-----|-----|----------|
| 44 | 651784 | histone H2A.X [Homo sapiens] >pir S07631 S07631 histone H2A.X - human >sp P16104 H2AX_HUMAN HISTONE H2A.X. {SUB 2-143} Length = 143 | gil31973 | 2 | 514 | 98 | 98 | HKGA194 |
| 45 | 651826 | keratin, 5SK type II cytoskeletal - human (fragment) Length = 489 | pir B24177 B 24177 | 2 | 1300 | 86 | 86 | HN-TAH42 |
| 46 | 653282 | phosphate transfer protein B precursor, mitochondrial - bovine Length = 361 | pir D53737 D 53737 | 30 | 392 | 90 | 90 | HCFNY90 |
| 47 | 657122 | | | 1 | 204 | | | IKGAQ13 |
| 48 | 661442 | rab1B protein (AA 1 - 201) [Rattus sp.] Length = 201 | gil57006 | 1 | 672 | 98 | 99 | IICHM133 |
| 49 | 664914 | phosphotyrosyl phosphatase activator [Oryctolagus cuniculus] >pir B54021 B54021 phosphotyrosyl phosphatase activator PTPA - rabbit >sp Q28717 Q28717 PHOSPHOTYROSYL PHOSPHATASE ACTIVATOR. Length = 323 | gil509144 | 1 | 228 | 98 | 100 | HEGAK11 |
| 50 | 666654 | | | 63 | 395 | | | HOFNL37 |
| 51 | 667084 | cytokeratin 17 [Homo sapiens] >gil34075 keratin related product [Homo sapiens] >pir S30433 S30433 keratin 17, cytoskeletal - human >sp Q04695 K1CQ_HUMAN KERATIN, TYPE I CYTOSKELETAL 17 (CYTOKERATIN 17) (K17) (CK 17) (39.1) (VERSION 1). {SUB 2-432} Length | gil30379 | 3 | 1379 | 100 | 100 | HKADA74 |

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|----|--------|---|------------------|-----|------|-----|-----|---------|
| 52 | 667380 | cell surface glycoprotein [Homo sapiens] >gnl PID d1006754 TALLA-1 [Homo sapiens] >gnl PID d1001976 cell surface glycoprotein [Homo sapiens] >pir 139368 139368 T-cell acute lymphoblastic leukemia associated antigen 1 - human >sp P41732 A15_HUMAN CELL SURF | gnl PID d1001976 | 1 | 474 | 100 | 100 | HMIBK53 |
| 53 | 669530 | | | 264 | 440 | | | HPFCJ30 |
| 54 | 671315 | cell cycle checkpoint control protein [Homo sapiens] >sp Q99638 Q99638 CELL CYCLE CHECKPOINT CONTROL PROTEIN. Length = 391 | gij 1765956 | 320 | 1279 | 92 | 92 | HDABE95 |
| 55 | 671993 | NAD(H)-specific isocitrate dehydrogenase gamma-subunit precursor [Homo sapiens] >gnl PID e219959 NAD (H)-specific isocitrate dehydrogenase gamma subunit precursor [Homo sapiens] >gij 1302655 NAD+-isocitrate dehydrogenase gamma subunit [Homo sapiens] >gij 40 | gnl PID e211919 | 1 | 993 | 91 | 91 | HSJCA89 |
| 56 | 674618 | | | 223 | 312 | | | HOVBX22 |
| 57 | 675027 | | | 789 | 1160 | | | HSDI169 |
| 58 | 677202 | vimentin [Homo sapiens] >sp Q15867 Q15867 VIMENTIN (FRAGMENT). Length = 354 | gij 340232 | 705 | 896 | 100 | 100 | HWACG51 |

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|----|--------|--|---------------------|-----|------|-----|-----|-----------|
| 59 | 678504 | ORF YGR031w [Saccharomyces cerevisiae] >pir[S64322]S64322 probable membrane protein YGR031w - yeast (Saccharomyces cerevisiae) Length = 342 | gnl PID e2432 77 | 320 | 640 | 38 | 63 | HCHAG27 |
| 60 | 678985 | 54 kDa protein [Homo sapiens] >gnl PID e124514 p54nrb [Homo sapiens] >pir G01211 G01211 54 kDa protein - human >sp Q12786 Q12786 54 KDA PROTEIN. Length = 471 (AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gij3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358 | gij407308 | 358 | 1203 | 100 | 100 | HCHOL54 |
| 61 | 682161 | (AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gij3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358 | gij2920585 | 3 | 869 | 89 | 89 | HCHAG19 |
| 62 | 683476 | | | 1 | 132 | | | HOFMM27 |
| 63 | 691146 | KDEL receptor [Homo sapiens] >pir S13293 S13293 KDEL receptor - human >sp P24390 ER21_HUMAN ER LUMEN PROTEIN RETAINING RECEPTOR 1 (KDEL RECEPTOR 1). Length = 212 | gij34031 | 1 | 372 | 100 | 100 | IIDAIB302 |
| 64 | 693589 | | | 1 | 393 | | | HCHAS12 |

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|----|--------|--|---------------------|-----|------|----|----|----|----------|
| 65 | 694991 | B4B gene product [Homo sapiens] >gnl PID e265628 progression associated protein [Homo sapiens] >gij 1932786 epithelial membrane protein [Homo sapiens] >gij 2506160 TMP [Homo sapiens] >sp P54849 EMPI_HUMAN EPITHELIAL MEMBRANE PROTEIN-1 (EMP-1) (TUMOR-ASSOCIA | gnl PID e1949 46 | 1 | 663 | 98 | 98 | 98 | HRAAY77 |
| 66 | 698303 | heat shock factor 1 [Homo sapiens] >pir A41137 A41137 heat shock transcription factor 1 - human >sp Q00613 HSF1_HUMAN HEAT SHOCK FACTOR PROTEIN 1 (HSF 1) (HEAT SHOCK TRANSCRIPTION FACTOR 1) (HSTF 1). Length = 529 filamin [Homo sapiens] Length = 2647 | gij 184403 | 23 | 1168 | 85 | 85 | 85 | HSHCA55 |
| 67 | 698669 | | gij 1203969 | 27 | 1274 | 98 | 98 | 98 | HEGAR20 |
| 68 | 705696 | | | 321 | 458 | | | | HOFMP28 |
| 69 | 706393 | vacuolar H+ ATPase proton channel subunit [Homo sapiens] >pir A39367 A39367 H+- transporting ATPase (EC 3.6.1.35) chain PKDI - human Length = 155 | gij 189676 | 119 | 604 | 84 | 84 | 85 | HSKHIP64 |
| 70 | 707357 | | | 3 | 344 | | | | HOFMM35 |

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|----|--------|--|----------------|-----|------|-----|-----|---------|
| 71 | 707360 | leucine aminopeptidase, LAP [cattle, kidney, Peptide, 513 aa] [Bos taurus] >pir A54338 APBOL leucyl aminopeptidase (EC 3.4.11.1), renal - bovine >sp P00727 AMPL_BOVIN CYTOSOL AMINOPEPTIDASE (EC 3.4.11.1) (LEUCINE AMINOPEPTIDASE) (LAP) (LEUCYL AMINOPEPTIDASE) serine/threonine protein kinase [Homo sapiens] >pir S23385 S23385 protein kinase (EC 2.7.1.37) cdc2-related PCTAIRE-1 - human >sp Q00536 KPT1_HUMAN SERINE/THREONINE-PROTEIN KINASE PCTAIRE-1 (EC 2.7.1.-) >sp G252370 G252370 CDC2-RELATED PROTEIN KINASE {CL | bbs 137417 | 1 | 447 | 81 | 89 | HOF35 |
| 72 | 707375 | serine/threonine protein kinase [Homo sapiens] >pir S23385 S23385 protein kinase (EC 2.7.1.37) cdc2-related PCTAIRE-1 - human >sp Q00536 KPT1_HUMAN SERINE/THREONINE-PROTEIN KINASE PCTAIRE-1 (EC 2.7.1.-) >sp G252370 G252370 CDC2-RELATED PROTEIN KINASE {CL | gi 36619 | 2 | 1582 | 92 | 92 | HTOJQ73 |
| 73 | 707754 | | | 2 | 376 | | | HLD45 |
| 74 | 711172 | | | 237 | 395 | | | HCV40 |
| 75 | 712248 | transcription factor AP-2 beta [Homo sapiens] >sp E286536 E286536 TRANSCRIPTION FACTOR AP-2 BETA. Length = 367 | gn P1D e286536 | 99 | 344 | 100 | 100 | HKGW94 |
| 76 | 715445 | DNA-PK [Homo sapiens] >pir G02083 G02083 DNA-PK - human (fragment) >sp Q13337 Q13337 DNA-PK (FRAGMENT). Length = 930 | gi 1017757 | 119 | 988 | 99 | 99 | HL107 |
| 77 | 716362 | | | 221 | 688 | | | HBC77 |

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|----|--------|--|----------------|-----|------|-----|-----|----------|
| 78 | 716835 | (AF036241) Na+/H+ exchange regulatory co-factor [Homo sapiens] >gi 3220019 (AF015926) ezrin-radixin-moesin binding phosphoprotein-50 [Homo sapiens] >sp O14745 O14745 EZRIN-RADIXIN-MOESIN BINDING PHOSPHOPROTEIN-50. Length = 358 | gi 2920585 | 3 | 755 | 79 | 79 | HCHA181 |
| 79 | 716947 | SRp55-2 [Homo sapiens] Length = 135 | gi 1049084 | 2 | 145 | 100 | 100 | HADDY71 |
| 80 | 717685 | alpha-mannosidase [Homo sapiens] Length = 987 | gi 1419374 | 2 | 1120 | 99 | 99 | IIDPUO15 |
| 81 | 719755 | | | 89 | 802 | | | HCGACS4 |
| 82 | 720389 | inducible membrane protein [Homo sapiens] >gi 806806 cell surface glycoprotein [Homo sapiens] >gi 1832296 metastasis suppressor [Homo sapiens] >pir 38942 A46493 metastasis suppressor KAI1 - human >sp P27701 CD82_HUMAN CD82 ANTIGEN (INDUCIBLE MEMBRANE PRO | gi 35833 | 1 | 594 | 65 | 67 | HUVCR41 |
| 83 | 720903 | cDNA isolated for this protein using a monoclonal antibody directed against the p27k prosomal protein [Homo sapiens] Length = 266 | gnl PIDe103161 | 108 | 614 | 93 | 95 | HFV1H35 |

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|----|--------|--|---------------------|-----|------|----|----|----------|
| 84 | 721348 | G6PD (AA 1-515) [Homo sapiens] >sp P11413 G6PD_HUMAN GLUCOSE-6- PHOSPHATE 1-DEHYDROGENASE (EC 1.1.1.49) (G6PD). {SUB 2-515} >gi 439445 glucose-6-phosphate dehydrogenase [Didelphis virginiana] {SUB 258-288} >sp O46666 O46666 GLUCOSE-6- PHOSPHATE DEHYDROGENAS | gi 31543 | 545 | 2065 | 93 | 93 | HSHBL14 |
| 85 | 721562 | pescadillo [Homo sapiens] >sp O00541 O00541 PESCADILLO. Length = 588 | gi 2194203 | 32 | 811 | 99 | 99 | HCICK84 |
| 86 | 722775 | | | 409 | 1680 | | | HCHAD52 |
| 87 | 724463 | | | 126 | 335 | | | HOFMP50 |
| 88 | 727501 | SWI/SNF complex 170 KDa subunit [Homo sapiens] >sp Q92923 Q92923 SWI/SNF COMPLEX 170 KDA SUBUNIT. Length = 1213 | gi 1549241 | 1 | 1302 | 97 | 97 | HL YBV46 |
| 89 | 728418 | GTP binding protein [Mus musculus] >pir A39611 A39611 probable GTP-binding protein - mouse >sp P23249 MV10_MOUSE PROTEIN MOV-10. >gi 433685 gb 110 /Mov 10 locus gene product [Mus musculus] {SUB 1-45} Length = 1004 | gi 53169 | 3 | 911 | 93 | 96 | HSSEP09 |
| 90 | 728920 | adipophilin [Homo sapiens] >sp Q99541 Q99541 ADIPOPHILIN (FRAGMENT). Length = 437 | gnl P1D1e2927 52 | 2 | 751 | 89 | 89 | HLDQRQ71 |
| 91 | 732958 | | | 3 | 296 | | | HPTTYA52 |

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|-----|--------|---|---------------------|-----|------|-----|-----|---------|
| 92 | 733134 | NF45 protein [Homo sapiens] >pir A54857 A54857 transcription factor NF-AT 45K chain - human >sp Q12905 Q12905 NF45 PROTEIN. Length = 406 | gil532313 | 84 | 1259 | 100 | 100 | HHBHP80 |
| 93 | 734099 | | | 150 | 365 | | | HBGDI44 |
| 94 | 734599 | | | 163 | 705 | | | H6EED05 |
| 95 | 736019 | ribosomal protein L11 [Homo sapiens] >gil57678 ribosomal protein L11 [Rattus rattus] >pir S17351 R5RT11 ribosomal protein L11 precursor - rat >sp G3115334 G3115334 RIBOSOMAL PROTEIN L11. >sp D1026769 D1026769 RIBOSOMAL PROTEIN L11 (FRAGMENT). {SUB 17-52} | gil3115334 | 3 | 608 | 100 | 100 | HSEBB02 |
| 96 | 738268 | | | 45 | 233 | | | HE2OC41 |
| 97 | 738911 | (AF069291) hT41 [Homo sapiens] >sp G3687829 G3687829 HT41. Length = 505 | gil3687829 | 3 | 656 | 40 | 62 | HCHC112 |
| 98 | 739226 | | | 3 | 125 | | | HADFY59 |
| 99 | 739527 | | | 3 | 752 | | | HACCL62 |
| 100 | 740710 | acyl-CoA synthetase-like protein [Homo sapiens] Length = 670 | gnl PID e3212 96 | 8 | 307 | 96 | 100 | HPMFQ72 |

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|-----|--------|--|------------------------|------|------|-----|-----|----------|
| 101 | 742980 | serine-threonine specific protein phosphatase [Homo sapiens] >sp E1334695 E1334695 SERINE- THREONINE SPECIFIC PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 317 | gn P D e 1334 695 | 3 | 182 | 81 | 86 | HSKCE51 |
| 102 | 744331 | ZINC FINGER PROTEIN {N- TERMINAL}. Length = 77 | sp G632682 G 632682 | 432 | 791 | 62 | 80 | HCHAH75 |
| 103 | 744751 | collagen alpha 3(VI) chain precursor - human Length = 2970 | pir S13679 C GHU3A | 902 | 1189 | 100 | 100 | HUFFV63 |
| 104 | 745750 | | | 349 | 714 | | | HCEIIX66 |
| 105 | 746285 | | | 2016 | 2297 | | | HINTNQ78 |
| 106 | 746416 | (AB013357) 49 kDa zinc finger protein [Mus musculus] Length = 460 | gn P D d 103 8083 | 113 | 391 | 97 | 97 | HOIOMO90 |
| 107 | 747851 | (AF035387) C7-1 protein [Rattus norvegicus] >sp O54715 O54715 C7-1 PROTEIN. Length = 463 | gi 2655418 | 3 | 974 | 78 | 80 | HSSJG21 |
| 108 | 750632 | | | 252 | 449 | | | HOGBF68 |
| 109 | 751315 | | | 423 | 608 | | | HLTGN10 |
| 110 | 754009 | | | 408 | 773 | | | HE8PN81 |
| 111 | 754634 | | | 525 | 1070 | | | HUSGH70 |
| 112 | 756637 | (AF044127) peroxisomal short-chain alcohol dehydrogenase [Homo sapiens] >sp G4105190 G4105190 PEROXISOMAL SHORT-CHAIN ALCOHOL DEHYDROGENASE. Length = 260 | gi 4105190 | 38 | 586 | 89 | 91 | HMWTY27 |

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|-----|--------|--|--------------------|-----|-----|-----|----------|
| 113 | 756833 | | | 1 | 387 | | HCEDP17 |
| 114 | 756878 | | | 127 | 399 | | IIIBDE92 |
| 115 | 757332 | cyto keratin 8 [Homo sapiens] >gi 553163 keratin 8 [Homo sapiens] {SUB 1-231} Length = 482 | gi 181573 | 35 | 235 | 100 | HOFM152 |
| 116 | 760835 | Pectinase gene transcriptional regulator. [Escherichia coli] >gnl PID1015936 Pectinase gene transcriptional regulator. [Escherichia coli] >gi 1787806 (AE000250) putative transcriptional regulator LYSR- type [Escherichia coli] >pir A64907 A64907 hypotheti | gnl PID101 5928 | 3 | 434 | 100 | HE9BW44 |
| 117 | 761760 | F45G2.10 [Caenorhabditis elegans] >sp O62252 O62252 F45G2.10 PROTEIN. Length = 160 | gnl PID1346 724 | 3 | 527 | 81 | HMWIF41 |
| 118 | 762520 | B-myb protein (AA 1-700) [Homo sapiens] >pir S01991 S01991 transforming protein B-myb - human >sp P10244 MYBB_HUMAN MYB- RELATED PROTEIN B (B-MYB). Length = 700 | gi 29472 | 77 | 520 | 100 | HBJJB76 |
| 119 | 764461 | | | 2 | 211 | | HOFMH95 |
| 120 | 764517 | phosphomevalonate kinase [Homo sapiens] >sp Q15126 PMKA_HUMAN PHOSPHOMEVALONATE KINASE (EC 2.7.4.2) (PMKASE). {SUB 2-192} >gi 3445542 (AF026069) phosphomevalonate kinase [Homo sapiens] {SUB 33-192} Length = 192 | gi 1294782 | 260 | 877 | 100 | HCGAA73 |

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|-----|--------|--|-------------------|------|------|----|----|---------|
| 121 | 765132 | clk1; putative [Homo sapiens] >pir S5364 S5364 protein kinase clk1 (EC 2.7.1.-) - human >sp P49759 CLK1_HUMAN PROTEIN KINASE CLK1 (EC 2.7.1.-) (CLK). Length = 484 | gi 632964 | 1202 | 2251 | 99 | 99 | HE9QA05 |
| 122 | 765667 | (AF043250) mitochondrial outer membrane protein [Homo sapiens] >gi 3941347 (AF043253) mitochondrial outer membrane protein [Homo sapiens] >gi 4105703 (AF050154) D19S1177E [Homo sapiens] >sp G3941342 G3941342 MITOCHONDRIAL OUTER MEMBRANE PROTEIN. >sp G3941 | gi 3941342 | 144 | 1115 | 91 | 91 | HCHOB54 |
| 123 | 767113 | putative progesterone binding protein [Homo sapiens] >sp O00264 O00264 PUTATIVE PROGESTERONE BINDING PROTEIN. Length = 195 | gn PIDe3141 74 | 66 | 677 | 93 | 93 | HNTMW26 |
| 124 | 767204 | cytochrome P45011C4 [Oryctolagus cuniculus] >pir S20227 S20227 cytochrome P450 2C4 - rabbit (fragment) >sp Q29507 Q29507 CYTOCHROME P450 (EC 1.14.14.1) (FRAGMENT). Length = 145 | gi 64933 | 3 | 581 | 43 | 61 | HCHAN75 |
| 125 | 767400 | | | 2 | 1057 | | | HSYBI74 |

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|-----|--------|--|----------------------|-----|------|-----|-----|--------------------|
| 126 | 767962 | proteasome subunit C3 [Homo sapiens] >pir S15970 SNHUC3 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C3 - human >sp P25787 PRC3_HUMAN PROTEASOME COMPONENT C3 (EC 3.4.99.46) (MACROPAIN SUBUNIT C3) (MULTICATALYTIC ENDOPEPTIDASE COMPLEX SUBUNIT (AB002086) p47 [Rattus norvegicus] >gnl PID e294068 XY40 protein [Rattus norvegicus] >sp O35987 O35987 P47, COMPLETE CDS. Length = 370 adenine phosphoribosyltransferase [Homo sapiens] >gi 28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir S06232 RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp P07741 APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7) | gnl PID d100 1115 | 3 | 722 | 100 | 100 | HABAF63 |
| 127 | 768040 | (AB002086) p47 [Rattus norvegicus] >gnl PID e294068 XY40 protein [Rattus norvegicus] >sp O35987 O35987 P47, COMPLETE CDS. Length = 370 adenine phosphoribosyltransferase [Homo sapiens] >gi 28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir S06232 RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp P07741 APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7) | gnl PID d102 2509 | 119 | 661 | 84 | 89 | HSRDI53 |
| 128 | 769956 | adenine phosphoribosyltransferase [Homo sapiens] >gi 28819 adenine phosphoribosyltransferase (aprt) [Homo sapiens] >pir S06232 RTHUA adenine phosphoribosyltransferase (EC 2.4.2.7) - human >sp P07741 APT_HUMAN ADENINE PHOSPHORIBOSYLTRANSFERASE (EC 2.4.2.7) | gi 178867 | 2 | 592 | 100 | 100 | HIUFFC71 |
| 129 | 770133 | ALDH7 [Homo sapiens] >pir 138669 138669 ALDH7 - human >sp P43353 DHA7_HUMAN ALDEHYDE DEHYDROGENASE 7 (EC 1.2.1.5). >sp G601780 G601780 ALDH7. Length = 468 | gi 601780 | 958 | 1236 | 194 | 69 | HUSAX93 HCHAO38 |

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|-----|--------|---|----------------------|-----|------|-----|-----|----------|
| 131 | 771964 | (AD000092) human RAD23A homolog [Homo sapiens] >gnl PI D1005299 HHR23A protein [Homo sapiens] >pir S44443 S44443 RAD23 protein homolog2 - human Length = 363 | gi 1905912 | 29 | 1165 | 76 | 76 | HA MGD77 |
| 132 | 772582 | B-myb protein (AA 1-700) [Homo sapiens] >pir S01991 S01991 transforming protein B-myb - human >sp P10244 MYBB_HUMAN MYB- RELATED PROTEIN B (B-MYB). Length = 700 | gi 29472 | 150 | 974 | 99 | 99 | HYAAOS1 |
| 133 | 773387 | zinc finger protein [Homo sapiens] >pir I38620 I38620 zinc finger protein ZNF155 - human (fragment) Length = 139 | gi 495576 | 152 | 634 | 46 | 64 | HAJBC78 |
| 134 | 773827 | novel serine protease, PRSSI1 [Homo sapiens] >gnl PI D1014012 serin protease with IGF-binding motif [Homo sapiens] >sp Q92743 Q92743 NOVEL SERINE PROTEASE. Length = 480 | gnl PI D1e2751 86 | 3 | 1217 | 100 | 100 | HKADIF5 |
| 135 | 774108 | protein of unknown function [Homo sapiens] >pir C35826 C35826 hypothetical protein A, 13K - human >sp Q00994 HG74_HUMAN OVARIAN GRANULOSA CELL 13.0 KD PROTEIN HGR74. Length = 111 | gi 189379 | 303 | 623 | 75 | 75 | HEGAC01 |

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|-----|--------|--|---------------------|------|------|----|-----|----------|
| 136 | 774636 | glutathione transferase [Homo sapiens] >pir A39375 A39375 glutathione transferase (EC 2.5.1.18) class mu, GSTM2 - human >sp P28161 GTM2_HUMAN GLUTATHIONE S-TRANSFERASE MU 2 (EC 2.5.1.18) (GSTM2-2) (CLASS-MU). {SUB 2-218} >gnl PID e33921 glutathione transf | gil183301 | 61 | 747 | 98 | 98 | HI SDV78 |
| 137 | 775339 | SWI/SNF complex 60 KDa subunit [Homo sapiens] >sp Q92924 Q92924 SWI/SNF COMPLEX 60 KDA SUBUNIT. Length = 435 | gil1549243 | 3 | 320 | 98 | 100 | HSIGB35 |
| 138 | 775582 | | | 448 | 705 | | | HEPNB30 |
| 139 | 775779 | (AJ000332) Glucosidase II [Homo sapiens] >sp Q14697 Q14697 GLUCOSIDASE II PRECURSOR (KIAA0088). >gnl PID d1008224 The ha1225 gene product is related to human alpha- glucosidase. [Homo sapiens] {SUB 2-944} Length = 944 | gnl PID e3281 43 | 1 | 1695 | 98 | 98 | HLWAS86 |
| 140 | 777809 | cysteine-rich protein 2 [Homo sapiens] >gnl PID d1008288 ESI1/CRP2 [Homo sapiens] >pir G02090 G02090 cysteine-rich protein 2 - human >sp P52943 CRP2_HUMAN CYSTEINE- RICH PROTEIN 2 (CRP2) (ESI1 PROTEIN). Length = 208 | gil1399028 | 202 | 681 | 99 | 100 | HSPMB57 |
| 141 | 778927 | valyl-tRNA synthetase [Homo sapiens] >pir S17675 S17675 valine--tRNA ligase (EC 6.1.1.9) - human Length = 1265 | gil31545 | 1843 | 3282 | 88 | 88 | HIMVBW39 |

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|-----|--------|--|-----|------|-----|-----------|
| 142 | 779262 | | 1 | 288 | | HTENK29 |
| 143 | 779392 | | 2 | 181 | | HE2FO87 |
| 144 | 780149 | proteasome activator hPA28 suunit beta [Homo sapiens] >pir I53518 I53518 proteasome activator hPA28 suunit beta - human >sp Q15129 Q15129 PROTEASOME ACTIVATOR HPA28 SUUNIT BETA. >sp G693763 G693763 PA28=REGULATORS OF THE 20 S PROTEASOME {PEPTIDE 15}. {SUB | 233 | 955 | 93 | HSPMF83 |
| 145 | 780583 | | 8 | 607 | | HHIEW04 |
| 146 | 780960 | | 232 | 576 | | HOEBN65 |
| 147 | 781469 | radixin [Homo sapiens] >pir A46127 A46127 radixin - human Length = 583 | 1 | 303 | 100 | HNTRA25 |
| 148 | 781556 | | 116 | 190 | | HOSAW82 |
| 149 | 781771 | | 1 | 822 | | HESEO05 |
| 150 | 782033 | histone H2A [Gallus gallus] Length = 129 | 146 | 544 | 98 | HU...CC66 |
| 151 | 782105 | | 606 | 1064 | 100 | HKAKV16 |

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|-----|--------|--|----------------------|-----|------|----|----|----------|
| 152 | 782122 | high density lipoprotein binding protein [Homo sapiens] >pir A44125 A44125 high density lipoprotein-binding protein, 110K - human >sp Q00341 HBP_HUMAN HIGH DENSITY LIPOPROTEIN BINDING PROTEIN (HDL-BINDING PROTEIN). >sp G1478463 G1478463 VIGILIN=KH PROTEIN | gil183892 | 3 | 983 | 95 | 95 | HSRAB32 |
| 153 | 783135 | zinc finger protein [Homo sapiens] >sp O00488 O00488 ZINC FINGER PROTEIN. Length = 116 | gnl P1D1d102 1201 | 3 | 500 | 97 | 99 | HCHCB61 |
| 154 | 783245 | | | 3 | 341 | | | H1TSFV77 |
| 155 | 783247 | | | 95 | 391 | | | HBCMDI8 |
| 156 | 783413 | D9 splice variant 3 [Mus musculus] >sp O08695 O08695 D9 SPLICE VARIANT 3. Length = 169 | gil2071991 | 1 | 591 | 80 | 88 | HEBFR23 |
| 157 | 784407 | | | 45 | 185 | | | HFKAA09 |
| 158 | 784548 | nuclear RNA helicase (DEAD family) [Homo sapiens] >pir I37201 I37201 nuclear RNA helicase (DEAD family) BAT1 - human >sp Q13838 HE47_HUMAN PROBABLE ATP-DEPENDENT RNA HELICASE P47. >gil2739119 (AF029061) BAT1 [Homo sapiens] {SUB 145-428} >gil971677 express | gil587146 | 676 | 1020 | 90 | 92 | HSRFGZ85 |

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|-----|--------|--|----------------------|-----|------|----|-----|-----|------------|
| 159 | 785075 | KIAA0100 is a human counterpart of mouse e1 gene. [Homo sapiens] >sp Q14667 Q14667 KIAA0100 (HUMAN COUNTERPART OF MOUSE E1 GENE). Length = 2092 | gnl PID d100 8477 | 72 | 1109 | 93 | 93 | 93 | HDPEX40 |
| 160 | 785677 | (AC004084) similar to DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE; 98% similar to P5243 (PID:g1710661) [Homo sapiens] >sp O43375 O43375 SIMILAR TO DNA-DIRECTED RNA POLYMERASE II 13.3 KD POLYPEPTIDE (FRAGMENT). Length = 105 | gil 2822158 | 1 | 273 | 95 | 100 | 100 | HBSAJ50 |
| 161 | 786238 | | | 2 | 994 | | | | HOVCA75 |
| 162 | 786389 | | | 3 | 1124 | | | | IIJ1J1J1J1 |
| 163 | 786929 | (AJ224442) methyltransferase [Homo sapiens] >sp O43709 O43709 METHYLTRANSFERASE. Length = 220 PIPPin protein [Rattus norvegicus] >pir JC4588 JC4588 RNA-binding protein PIPPin - rat >sp Q63430 Q63430 PIPPIN PROTEIN. Length = 154 | gnl PID e1253 426 | 123 | 404 | 86 | 95 | 95 | IIJ1NV27 |
| 164 | 786932 | | gil 1050754 | 2 | 490 | 76 | 87 | 87 | HUSYH27 |
| 165 | 787078 | HER2 receptor [Homo sapiens] >gil 553282 c-erb-2 protein [Homo sapiens] {SUB 737-1031} >gil 553332 HER-2/neu [Homo sapiens] {SUB 1-191} >gil 183989 HER2 receptor (AA at 3) [Homo sapiens] {SUB 740-910} >gil 182169 c-erb B2/neu protein [Homo sapiens] {SUB 1081-} | gil 306840 | 236 | 1114 | 79 | 79 | 79 | HCHND12 |

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|-----|--------|--|-----------------------|-----|------|----|----------|
| 166 | 787139 | | | 230 | 625 | | HBCBA06 |
| 167 | 787283 | | | 3 | 656 | | HFOYO96 |
| 168 | 788761 | MAL3P6.24 [Plasmodium falciparum] >sp O7737 O7737 MAL3P6.24 PROTEIN. Length = 1017 | gnl PID e 1331 909 | 2 | 700 | 36 | HTXFK57 |
| 169 | 788988 | (AF023611) Dim1p homolog [Homo sapiens] >sp O14834 O14834 DIM1P HOMOLOG. Length = 142 | gi 2565275 | 70 | 417 | 98 | HUSGH90 |
| 170 | 789092 | | | 2 | 400 | | H6EBE80 |
| 171 | 789298 | (AF044311) gamma-synuclein [Homo sapiens] >gi 3642775 (AF017256) persyn [Homo sapiens] >gi 3642903 (AF037207) persyn [Homo sapiens] >sp O76070 O76070 PERSYN. Length = 127 | gi 3347842 | 1 | 489 | 82 | HTSFM20 |
| 172 | 789299 | | | 205 | 381 | | HBGDD91 |
| 173 | 789718 | | | 233 | 580 | | IIBGBT30 |
| 174 | 789957 | beta-hexosaminidase alpha chain [Homo sapiens] >pir A23561 AOHUBA beta-N- acetylhexosaminidase (EC 3.2.1.52) alpha chain precursor - human >sp P06865 HEXA_HUMAN BETA- HEXOSAMINIDASE ALPHA CHAIN PRECURSOR (EC 3.2.1.52) (N-ACETYL- BETA-GLUCOSAMINIDASE) (BETA- | gi 179458 | 750 | 1619 | 99 | HISEM44 |

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|-----|--------|--|------------|-----|------|-----|-----|---------|
| 175 | 789977 | arginyl-tRNA synthetase, ArgRS [human, ataxia-telangiectasia patients, EBV-lymphoblastoid cells, Peptide, 659 aa] [Homo sapiens] >pir JC4365 JC4365 arginine--tRNA ligase (EC 6.1.1.19) - human Length = 659 | bbs 173838 | 25 | 2019 | 94 | 95 | HMEIU30 |
| 176 | 790285 | HCG V [Homo sapiens] >sp O60927 O60927 HCG V. Length = 126 | gi 3176438 | 44 | 391 | 85 | 85 | HDPCH88 |
| 177 | 790509 | human elongation factor-1-delta [Homo sapiens] >pir S34626 S34626 translation elongation factor eEF-1 delta chain - human >sp P29692 EF1D_HUMAN ELONGATION FACTOR 1-DELTA (EF-1-DELTA). Length = 281 | gi 38522 | 227 | 1108 | 63 | 64 | HPMGB64 |
| 178 | 790775 | | | 950 | 1351 | | | HJAAO21 |
| 179 | 790888 | (AF036956) neuroblastoma apoptosis-related RNA binding protein [Homo sapiens] >sp G4104559 G4104559 NEUROBLASTOMA APOPTOSIS-RELATED RNA BINDING PROTEIN. Length = 490 | gi 4104559 | 2 | 274 | 100 | 100 | HE3QE19 |
| 180 | 791506 | | | 2 | 205 | | | HOFMB93 |
| 181 | 791649 | | | 3 | 359 | | | HBCBH10 |
| 182 | 791802 | | | 165 | 695 | | | HWLRH03 |

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|-----|--------|--|-----------|-----|------|-----|-----|---------|
| 183 | 792002 | ADP-ribosylation factor [Homo sapiens] >gi2088529 ADP-ribosylation factor 5 [Homo sapiens] >gi438870 ADP- ribosylation factor 5 [Rattus norvegicus] >gnlPIDid1014187 ARF5 [Mus musculus] >pirA23741A23741 ADP-ribosylation factor 5 - human >pirJC4949JC4 | gi1178987 | 2 | 655 | 100 | 100 | HHENT53 |
| 184 | 792291 | see GenBank Accession Number U01184 for cDNA; similar to Drosophila melanogaster flil in GenBank Accession Number U01182 and Caenorhabditis elegans flil homolog in GenBank Accession Number U01183 [Homo sapiens] >spQ13045Q13045 FLIGHTLESS-1 PROTEIN HOMOL | gi2138290 | 843 | 3329 | 96 | 96 | HDPIT69 |
| 185 | 792371 | | | 3 | 665 | | | HUSJW77 |
| 186 | 792660 | (AF044773) breakpoint cluster region protein 1 [Homo sapiens] >spQ60558Q60558 BREAKPOINT CLUSTER REGION PROTEIN 1. Length = 138 | gi3002951 | 116 | 406 | 100 | 100 | HCHMC26 |
| 187 | 792782 | | | 41 | 838 | | | HTXJB38 |
| 188 | 792890 | (AF001846) lymphoid phosphatase LyP1 [Homo sapiens] >spG4100632G4100632 LYMPHOID PHOSPHATASE LYPI. Length = 808 | gi4100632 | 2 | 994 | 90 | 90 | HHESJ29 |
| 189 | 792931 | | | 1 | 576 | | | HEGAW71 |

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|-----|--------|--|-----------------------|------|------|-----|-----|----------|
| 190 | 792943 | myosin heavy chain kinase B [Dictyostelium discoideum] >sp P90648 KMHIB_DICDI MYOSIN HEAVY CHAIN KINASE B (EC 2.7.1.129) (MHCK B). Length = 732 | gi 1903458 | 3 | 1247 | 43 | 68 | IIDPRZ79 |
| 191 | 793104 | | | 107 | 250 | | | HKGAJ80 |
| 192 | 793445 | desmoyokin - human (fragments) >sp Q09666 AHNK_HUMAN NEUROBLAST DIFFERENTIATION ASSOCIATED PROTEIN AHNK (DESMOYOKIN) (FRAGMENTS). >gi 178281 AHNAK_nucleoprotein [Homo sapiens] {SUB 1-1683} >gi 897824 AHNAK gene product [Homo sapiens] {SUB 1684-2960} Leng | pir A45259 A 45259 | 1 | 723 | 92 | 92 | HDTEJ86 |
| 193 | 793446 | | | 25 | 255 | | | HIIBGY94 |
| 194 | 793639 | (AF044959) NADH:ubiquinone oxidoreductase NDUFS6 subunit [Homo sapiens] >sp O75380 NUMM_HUMAN NADH-UBIQUINONE OXIDOREDUCTASE 13 KD-A SUBUNIT PRECURSOR (EC 1.6.5.3) (EC 1.6.99.3) (COMPLEX I-13KD-A) (CI-13KD-A). Length = 124 | gi 3348137 | 1 | 411 | 100 | 100 | HLJB172 |
| 195 | 794213 | 100 kDa protein [Rattus norvegicus] >pir S22659 S22659 hypothetical protein, 100K - rat >sp Q62671 100K_RAT 100 KD PROTEIN (EC 6.3.2.-). Length = 889 | gi 55535 | 326 | 691 | 93 | 95 | HLWCN67 |
| 196 | 795858 | | | 1020 | 1205 | | | HLVDY53 |

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|-----|--------|--|----------------------|-----|------|-----|-----|---------|
| 197 | 795955 | c-myc binding protein [Homo sapiens] >sp Q99471 MM1_HUMAN C-MYC BINDING PROTEIN MM-1. >sp D1014706 D1014706 C-MYC BINDING PROTEIN. Length = 167 ribosomal protein L7a large subunit [Homo sapiens] >gi 34203 L7a protein [Homo sapiens] >gi 35512 PLA-X polypeptide [Homo sapiens] >gi 36647 ribosomal protein L7a [Homo sapiens] >gi 56956 ribosomal protein L7a (AA 1-266) [Rattus rattus] >pir S19717 R5HU7A | gnl PID d101 4706 | 31 | 507 | 100 | 100 | HUSXX36 |
| 198 | 796359 | ribosomal protein L7a large subunit [Homo sapiens] >gi 34203 L7a protein [Homo sapiens] >gi 35512 PLA-X polypeptide [Homo sapiens] >gi 36647 ribosomal protein L7a [Homo sapiens] >gi 56956 ribosomal protein L7a (AA 1-266) [Rattus rattus] >pir S19717 R5HU7A | gi 337495 | 19 | 297 | 100 | 100 | HOFNW79 |
| 199 | 796555 | DJ366N23.3 (K1AA0173 AND TUBULIN- TYROSINE LIGASE LIKE) (FRAGMENT). Length = 278 PEG1/MEST [Homo sapiens] >sp O15007 O15007 PEG1/MEST GENE MRNA. Length = 335 (AF022229) translation initiation factor 6 [Homo sapiens] >gnl PID e304603 b4 integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gen homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT | sp O75653 O7 5653 | 1 | 1086 | 44 | 62 | HLWEW04 |
| 200 | 796675 | PEG1/MEST [Homo sapiens] >sp O15007 O15007 PEG1/MEST GENE MRNA. Length = 335 (AF022229) translation initiation factor 6 [Homo sapiens] >gnl PID e304603 b4 integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gen homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT | gnl PID e3070 37 | 44 | 1027 | 100 | 100 | HSICR25 |
| 201 | 796743 | (AF022229) translation initiation factor 6 [Homo sapiens] >gnl PID e304603 b4 integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gen homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT | gi 2809383 | 30 | 842 | 100 | 100 | H6EDUI2 |
| 202 | 796792 | integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gen homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT | | 198 | 461 | | | HDTII72 |
| 203 | 799668 | integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gen homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT | | 166 | 303 | | | HODBC01 |
| 204 | 799669 | integrin interactor [Homo sapiens] >gi 3335506 (AF047433) b(2)gen homolog [Homo sapiens] >sp P56537 IF6_HUMAN EUKARYOTIC TRANSLATION INITIATION FACTOR 6 (EIF-6) (B4 INTEGRIN INT | | 2 | 310 | | | HOGAV29 |

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|-----|--------|---|-----|------|----|----------|
| 205 | 799673 | | 2 | 310 | | HOFMN53 |
| 206 | 799674 | | 130 | 1044 | | HCHMI60 |
| 207 | 799678 | ribosomal protein L18a [Homo sapiens] >gi 3702270 (AC005796) ribosomal protein L18a [Homo sapiens] >gnl P1D d1029536 (AB007175) ribosomal protein L18a [Homo sapiens] {SUB 111-176} Length = 176 | 40 | 345 | 98 | HOIFNL25 |
| 208 | 799728 | | 3 | 179 | | HBCBG75 |
| 209 | 799748 | | 1 | 660 | | HCTIMQ24 |
| 210 | 799760 | o361 [Escherichia coli] >gi 1790125 (AE000446) orf, hypothetical protein [Escherichia coli] >pir C65171 C65171 hypothetical 41.0 kD protein in ibpA-gyrB intergenic region - Escherichia coli (strain K-12) Length = 361 | 1 | 357 | 99 | IIBGBF66 |
| 211 | 799805 | | 2 | 118 | | HBGDA22 |
| 212 | 800296 | CDC37 homolog [Homo sapiens] >gi 1375485 CDC37 homolog [Homo sapiens] >pir G02313 G02313 CDC37 homolog - human >sp Q16543 Q16543 CDC37 HOMOLOG. Length = 378 | 2 | 802 | 89 | HIDABE68 |

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|-----|--------|--|------------|-----|------|-----|-----|---------|
| 213 | 800327 | ADP-ribosylation factor-like protein 2 [Homo sapiens] >pir A48259 A48259 ADP- ribosylation factor-like 2 - human >sp P36404 ARL2_HUMAN ADP- RIBOSYLATION FACTOR-LIKE PROTEIN 2. >sp G42565 G42565 ARL2=ADP-RIBOSYLATION FACTOR HOMOLOG. Length = 184 | gi 3009501 | 25 | 645 | 99 | 99 | HCHPQ4I |
| 214 | 800816 | | | 115 | 351 | | | HODCV09 |
| 215 | 800835 | (AF071538) Ets transcription factor PDEF [Homo sapiens] >sp G400741 G4007418 ETS TRANSCRIPTION FACTOR PDEF. Length = 335 | gi 4007418 | 3 | 881 | 96 | 96 | HETJP29 |
| 216 | 805429 | RanGAP1 [Homo sapiens] >pir JC5300 JC5300 Ran GTPase activator 1 - human Length = 587 | gi 575268 | 3 | 683 | 90 | 90 | HKABS06 |
| 217 | 805458 | (AF044221) HCG-1 protein [Homo sapiens] >sp G4105252 G4105252 HCG-1 PROTEIN. Length = 117 | gi 4105252 | 745 | 1122 | 100 | 100 | HDQEV55 |
| 218 | 805478 | | | 60 | 644 | | | HDQGR35 |
| 219 | 805805 | 19 kDa subunit of NADH:ubiquinone oxidoreductase complex (complex I) [Bos taurus] >pir S16208 S16208 NADH dehydrogenase (ubiquinone) (EC 1.6.5.3) 19K chain - bovine >sp P42029 NUPM_BOVIN NADH- UBIQUINONE OXIDOREDUCTASE 19 KD SUBUNIT (EC 1.6.5.3)(EC 1.6.99 | gi 599681 | 2 | 478 | 87 | 90 | HOFMH12 |
| 220 | 806486 | | | 3 | 62 | | | HFXJC33 |

interacting prote

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|-----|--------|--|----------------------|-----|------|-----|-----|----------|
| 229 | 815853 | calcyphosine [Homo sapiens] >gi 3075376 (AC004602) CAYP_HUMAN; RD25 [Homo sapiens] >sp Q13938 CAYP_HUMAN CALCYPHOSINE; Length = 189 S100 calcium-binding protein A13 (S100A13) [Homo sapiens] >pir JC5064 JC5064 S-100 calcium-binding protein A13 - human Length = 98 | gnl P D e2458 72 | 8 | 667 | 100 | 100 | HLHAY85 |
| 230 | 815999 | | gnl P D e2682 53 | 68 | 421 | 42 | 70 | HKABX07 |
| 231 | 823427 | | | 1 | 927 | | | HTLGL50 |
| 232 | 823704 | (AC004770) BC269730_2 [Homo sapiens] >sp O60427 O60427 BC269730_2. Length = 444 | gi 3169158 | 3 | 860 | 67 | 80 | HDAABC49 |
| 233 | 824798 | | | 307 | 858 | | | HDQCK75 |
| 234 | 825018 | | | 2 | 1924 | | | HETIS29 |
| 235 | 825076 | Whole ORF continues from bp19 (right after 'tag') to bp1596 ('iga'); similar to chinese hamster phosphatidylserine synthase. [Homo sapiens] Length = 473 | gnl P D d100 4031 | 2 | 1549 | 92 | 92 | HE9PJ48 |

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|-----|--------|---|--------------------------|-----|------|-----|-----|---------|
| 236 | 825787 | EXT2 [Homo sapiens] >gi162113 hereditary multiple exostoses gene 2 protein [Homo sapiens] >gi1519605 multiple exostosis 2 [Homo sapiens] >sp Q93063 EXT2_HUMAN EXOSTOSIN-2 (PUTATIVE TUMOUR SUPPRESSOR PROTEIN EXT2) (MULTIPLE EXOSTOSES PROTEIN 2). Length = | gi1518042 | 305 | 2293 | 100 | 100 | HEONV84 |
| 237 | 826116 | BETA CRYSTALLIN S (GAMMA CRYSTALLIN S). >gi557548 crystallin [Homo sapiens] {SUB 19-106} Length = 177 | sp P22914 CR BS_HUMAN | 392 | 682 | 86 | 87 | HAJAE27 |
| 238 | 826147 | neural specific protein CRMP-2 [Bos taurus] >sp O02675 DPY2_BOVIN DIHYDROPYRIMIDINASE RELATED PROTEIN-2 (DRP-2) (NEURAL SPECIFIC PROTEIN NSP60). Length = 572 | gi1916227 | 3 | 503 | 98 | 98 | HCEPT06 |
| 239 | 827020 | (AF027954) Bcl-2-related ovarian killer protein [Rattus norvegicus] >gi2689660 (AF027707) apoptosis activator Mtd [Mus musculus] >sp O35425 O35425 BCL-2- RELATED OVARIAN KILLER PROTEIN. Length = 213 | gi2645560 | 12 | 539 | 95 | 97 | HHFHE17 |
| 240 | 827586 | calmodulin [Plasmodium falciparum] >gi160128 calmodulin [Plasmodium falciparum] >pir B45594 MCZQF calmodulin - Plasmodium falciparum >sp P24044 CALM_PLAFA CALMODULIN. Length = 149 | gi385234 | 85 | 495 | 49 | 76 | HCHMW40 |

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|-----|--------|--|----------------------|-----|------|-----|-----|----------|
| 241 | 827732 | alternate name ygiG; ORF_f123 [Escherichia coli] >gij1789438 (AE000387) putative kinase [Escherichia coli] >pir H65093 H65093 ygiG protein - Escherichia coli (strain K-12) >sp P31055 FOLB_ECOLI PROBABLE DIHYDRONEOPTERIN ALDOLASE (EC 4.1.2.25) (DHNA). (SUB | gij 882580 | 181 | 282 | 91 | 95 | HBGDE81 |
| 242 | 827735 | | | 541 | 708 | | | HHEDU22 |
| 243 | 827740 | | | 716 | 838 | | | HBNAPI7 |
| 244 | 827808 | | | 86 | 1657 | | | HMELR44 |
| 245 | 828251 | (AB016869) p70 ribosomal S6 kinase beta [Homo sapiens] >sp D1035383 D1035383 P70 RIBOSOMAL S6 KINASE BETA. Length = 495 | gnl PID d103 5383 | 134 | 949 | 91 | 91 | INGOI.64 |
| 246 | 828357 | | | 1 | 768 | | | HK1YP61 |
| 247 | 828449 | | | 1 | 723 | | | HBXCZ22 |
| 248 | 828612 | syntaxin 5 [Homo sapiens] >pir G01817 G01817 syntaxin 5 - human Length = 301 | gij 886071 | 68 | 460 | 100 | 100 | HNHMY58 |
| 249 | 828647 | laminin beta 2 chain [Homo sapiens] >sp P55268 LMB2_HUMAN LAMININ BETA-2 CHAIN PRECURSOR (S- LAMININ). Length = 1798 | gnl PID e2132 86 | 299 | 2254 | 85 | 85 | HRABB47 |

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|-----|--------|--|----------------------|-----|------|----|----|---------|
| 250 | 828698 | galactokinase [Homo sapiens] >gi 1929895 galactokinase [Homo sapiens] >sp P51570 GALI_HUMAN GALACTOKINASE 1 (EC 2.7.1.6). >gi 3603423 (AF084935) galactokinase [Homo sapiens] {SUB 1-264} Length = 392 | gi 1002507 | 3 | 1220 | 83 | 83 | HKGAU37 |
| 251 | 828962 | secretory protein [Homo sapiens] >gi 940946 intestinal trefoil factor [Homo sapiens] >pir A48284 A48284 intestinal trefoil factor 3 precursor - human >sp Q07654 ITF_HUMAN INTESTINAL TREFOIL FACTOR PRECURSOR (HP1.B). Length = 80 | gi 402483 | 2 | 259 | 78 | 78 | HCHMR52 |
| 252 | 828982 | unnamed protein product [unidentified] >gi 189500 p62 [Homo sapiens] >pir A38219 A38219 GAP-associated tyrosine phosphoprotein p62 - human >sp Q07666 Q07666 GAP-ASSOCIATED TYROSINE PHOSPHOPROTEIN P62. >gnl PID e1259626 unnamed protein product [unidentified] | gnl PID e1259 622 | 1 | 1176 | 85 | 85 | HE9PCS2 |
| 253 | 829282 | | | 289 | 828 | | | HCHOB95 |
| 254 | 829368 | | | 279 | 512 | | | HWGAA79 |
| 255 | 829751 | | | 2 | 418 | | | HCHMB33 |
| 256 | 829773 | (AF109906) G9A [Mus musculus] >sp G3986768 G3986768 G9A. Length = 1000 | gi 3986768 | 26 | 862 | 97 | 98 | HMWBV67 |

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|-----|--------|---|----------------------|------|------|----|----|----------|
| 257 | 829934 | precursor polypeptide (AA -21 to 782) _ [Homo sapiens] >pir/A35954/A35954 endoplasmin precursor - human >sp P14625 ENPL_HUMAN ENDOPLASMIN PRECURSOR (94 KD GLUCOSE-REGULATED PROTEIN) (GRP94) (GP96 HOMOLOG) (TUMOR REJECTION ANTIGEN 1). Length = 803 dynamitin [Homo sapiens] >sp Q13561 DYNC_HUMAN DYNACTIN, 50 KD ISOFORM (50 KD DYNEIN-ASSOCIATED POLYPEPTIDE) (DYNAMITIN). Length = 406 | gi 37261 | 1142 | 2356 | 94 | 94 | HFIJ68 |
| 258 | 829942 | | gi 1255188 | 15 | 1409 | 85 | 85 | HUFBF69 |
| 259 | 829951 | | | 119 | 262 | | | HIBGBA32 |
| 260 | 830173 | death associated protein 5 [Homo sapiens] >sp O60877 O60877 DEATH ASSOCIATED PROTEIN 5. Length = 907 | gnl PIDle 298 888 | 51 | 2870 | 90 | 90 | HETIX39 |
| 261 | 830200 | | | 3 | 638 | | | HBGMF83 |
| 262 | 830365 | mevalonate pyrophosphate decarboxylase [Homo sapiens] >sp P53602 ER19_HUMAN DIPHOSPHOMEVALONATE DECARBOXYLASE (EC 4.1.1.33) (MEVALONATE PYROPHOSPHATE DECARBOXYLASE). Length = 400 | gi 1235682 | 56 | 1291 | 95 | 95 | HUSJC21 |
| 263 | 830456 | | | 215 | 397 | | | HCFBN01 |

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|-----|--------|--|---------------------|-----|------|-----|-----|---------|
| 264 | 830549 | guanine nucleotide-binding regulatory protein-beta-2 subunit [Homo sapiens] >gil33935 transducin beta-2 subunit [Homo sapiens] >gil3135310 (AF053356) GNB2 [Homo sapiens] >pir B26617 RGHUB2 GTP-binding regulatory protein beta-2 chain - human >sp P11016 GB | gil386751 | 1 | 729 | 100 | 100 | HDPM12 |
| 265 | 830602 | | | 24 | 461 | | | HTLDJ82 |
| 266 | 830610 | zyxin [Homo sapiens] >gnl PID e223417 zyxin [Homo sapiens] >pir G02845 G02845 zyxin - human Length = 572 | gnl PID e2182 60 | 956 | 1855 | 94 | 94 | HDPRN35 |
| 267 | 830644 | (AF104260) hiwi [Homo sapiens] >sp G4038413 G4038413 HIW1 (FRAGMENT). Length = 523 | gil4038413 | 2 | 391 | 99 | 99 | HTTEU95 |
| 268 | 830707 | | | 3 | 623 | | | HETCJ14 |
| 269 | 830709 | | | 2 | 304 | | | HSSGN20 |
| 270 | 830733 | | | 540 | 725 | | | HSNAD86 |
| 271 | 830768 | carboxylesterase hCE-2 [Homo sapiens] >sp Q16859 Q16859 CARBOXYLESTERASE (EC 3.1.1.1) (AL1-ESTERASE) (B-ESTERASE) (MONOBUTYRASE) (COCAINE ESTERASE) (PROCAINE ESTERASE) (METHYLBUTYRASE). Length = 550 | gil1407780 | 623 | 2269 | 99 | 99 | HDPEX44 |
| 272 | 830855 | | | 1 | 465 | | | HJPCE06 |

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|-----|--------|--|------|------|----|----------|
| 273 | 830949 | | 2457 | 2903 | | HCE3J35 |
| 274 | 830965 | | 139 | 792 | | HOIICAO1 |
| 275 | 830973 | | 354 | 557 | | HRDL42 |
| 276 | 830979 | THIOREDOXIN REDUCTASE 2. Length = 526 | 753 | 1454 | 81 | HOGCC93 |
| 277 | 830989 | La protein [Homo sapiens] >gi36415 ribonucleoprotein SS-B/La (AA 1-408) [Homo sapiens] >pirA31888/A31888 ribonucleoprotein La - human >spP05455/LA_HUMAN LUPUS LA PROTEIN (SJOGEN SYNDROME TYPE B ANTIGEN (SS-B)) (LA RIBONUCLEOPROTEIN) (LA AUTOANTIGEN). | 3 | 1382 | 87 | HDQFZ49 |
| 278 | 831134 | | 2 | 241 | | HBXEB46 |
| 279 | 831200 | | 3 | 773 | | HADXB20 |
| 280 | 831260 | | 892 | 1095 | | HLWBR58 |
| 281 | 831531 | transcription factor [Homo sapiens] >gi37058 IIB protein [Homo sapiens] >pirS17654/TWHU2B transcription initiation factor IIB - human >bbs112738 S300-II, TFII B=transcription factor [human, Peptide Partial, 311 aa] [Homo sapiens] (SUB 6-316) Length = 31 | 93 | 1172 | 95 | HHPGX85 |
| 282 | 831665 | | 2 | 1093 | | HSKDH81 |

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|-----|--------|---|-------------|------|------|----|-----|--|---------|
| 283 | 831724 | | | 1 | 468 | | | | HFEBQ94 |
| 284 | 831884 | (AF034800) liprin-alpha3 [Homo sapiens] >sp G3309535 G3309535 LIPRIN- ALPHA3 (FRAGMENT). Length = 443 | gij 3309535 | 20 | 469 | 90 | 90 | | HDTGO74 |
| 285 | 831897 | laminin B1 [Homo sapiens] >gij 186876 laminin B1 [Homo sapiens] >gij 186913 laminin B1 [Homo sapiens] >pir S13547 MMHUB1 laminin chain B1 precursor - human >sp P07942 LMB1_HUMAN LAMININ BETA-1 CHAIN PRECURSOR (LAMININ B1 CHAIN). Length = 1786 | gij 186837 | 1 | 1581 | 92 | 92 | | HSKHV84 |
| 286 | 831922 | | | 499 | 684 | | | | HDQIB68 |
| 287 | 831963 | | | 188 | 319 | | | | HDPGS84 |
| 288 | 832074 | gluconate kinase [Escherichia coli] >gij 1790719 (AE000497) gluconate kinase, thermosensitive glucokinase [Escherichia coli] >pir S56494 S56494 gluconokinase (EC 2.7.1.12) gntV - Escherichia coli >sp P39208 GNTV_ECOLI THERMOSENSITIVE GLUCONOKINASE (EC 2.7. | gij 537110 | 1 | 579 | 42 | 58 | | HCRNT71 |
| 289 | 832266 | | | 71 | 433 | | | | HNGJU70 |
| 290 | 832309 | | | 1891 | 2226 | | | | HBJDT21 |
| 291 | 832342 | fatty acid amide hydrolase [Homo sapiens] >sp O00519 O00519 FATTY ACID AMIDE HYDROLASE. Length = 579 | gij 2149156 | 9 | 224 | 97 | 100 | | HBGDP82 |

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|-----|--------|---|----------------------|-----|-----|-----|-----|---------|
| 292 | 832351 | unknown product specific to adipose tissue [Homo sapiens] >sp Q15847 Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76 | gnl PID d100 8821 | 47 | 298 | 68 | 68 | HFABE30 |
| 293 | 832352 | unknown product specific to adipose tissue [Homo sapiens] >sp Q15847 Q15847 HYPOTHETICAL 7.9 KD PROTEIN. Length = 76 | gnl PID d100 8821 | 89 | 277 | 92 | 94 | HOEKX93 |
| 294 | 832434 | Cks1 protein homologue [Homo sapiens] >pir A36670 A36670 protein kinase cdc2 complex subunit CKS1 - human >sp P33551 CKS1_HUMAN CYCLIN- DEPENDENT KINASES REGULATORY SUBUNIT 1 (CKS-1), Length = 79 growth arrest and DNA-damage-inducible protein [Homo sapiens] >gi 403128 [Human gadd45 gene, complete cds.], gene product [Homo sapiens] >pir A39617 A39617 DNA-damage-inducible protein gadd45 - human >sp P24522 GA45_HUMAN GROWTH ARREST AND DNA- DAMAGE-INDU | gi 29977 | 78 | 335 | 100 | 100 | HFNAB43 |
| 295 | 832490 | | gi 182940 | 220 | 798 | 98 | 100 | HKAKL21 |
| 296 | 832573 | | | 30 | 629 | | | HCHOY13 |
| 297 | 832580 | pS2 protein [Homo sapiens] >gi 35707 pS2 precursor [Homo sapiens] >gnl PID e223341 pS2 [Homo sapiens] >pir A26667 A26667 pS2 protein precursor - human >gi 182204 estrogen receptor [Homo sapiens] {SUB 2-84} Length = 84 | gi 35718 | 45 | 362 | 100 | 100 | H2LAR67 |

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|-----|--------|---|------------------|-----|------|----|-----|----------|
| 298 | 833394 | | | 274 | 588 | | | HIBGMC47 |
| 299 | 835355 | (AF060567) sushi-repeat protein [Homo sapiens] >sp O60687 O60687 SUSHI-REPEAT PROTEIN. Length = 465 | gij3108089 | 3 | 1295 | 99 | 100 | HUSAU05 |
| 300 | 835497 | (AJ006064) coronin-like protein [Rattus norvegicus] >sp O89046 O89046 CORONIN-LIKE PROTEIN. Length = 484 | gnl PID e1331790 | 334 | 1584 | 96 | 99 | HLDDS71 |
| 301 | 835728 | | | 2 | 871 | | | HODAK21 |
| 302 | 835978 | | | 643 | 2019 | | | ITLEB03 |
| 303 | 836091 | PDC-E2 precursor (AA -54 to 561) [Homo sapiens] >pir S01783 XXHU dihydrolipoamide S-acetyltransferase (EC 2.3.1.12) precursor - human (fragment) >gij345030 Human 70kd mitochondrial antigen of PBC [unidentified] {SUB 179-500} >sp G254062 G254062 PYRUVATE D | gij35360 | 546 | 2114 | 99 | 99 | I12CBW86 |
| 304 | 836274 | Id4 [Homo sapiens] >gnl PID e266418 helix-loop-helix protein [Homo sapiens] >gnl PID e1359205 (AL022726) dJ625H18.1 (ID4 Helix-loop-helix DNA binding protein) [Homo sapiens] >gnl PID e266418 helix-loop-helix protein [Homo sapiens] >pir G01855 G01855 Id4 - | gij881546 | 2 | 334 | 98 | 98 | HCLBP52 |

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|-----|--------|--|-----------------------|-----|------|-----|-----|---------|
| 305 | 836731 | (AF075599) ubiquitin conjugating enzyme 12 [Homo sapiens] >gnl PI D 1034111 (AB012191) Nedd8-conjugating enzyme hUbc12 [Homo sapiens] >sp O76069 O76069 UBIQUITIN- CONJUGATING ENZYME E2 (EC 6.3.2.19) (UBIQUITIN-PROTEIN LIGASE) (UBIQUITIN CARRIER PROTEIN). L prolyl 4-hydroxylase alpha (II) subunit [Homo sapiens] >sp O15460 O15460 PROLYL 4-HYDROXYLASE ALPHA (II) SUBUNIT (II). Length = 535 | gi 3309661 | 2 | 571 | 100 | 100 | HFXAZ01 |
| 306 | 838014 | | gi 2439985 | 3 | 1574 | 99 | 99 | HTEHY24 |
| 307 | 838874 | | | 271 | 546 | | | HFPEZ63 |
| 308 | 839120 | peptide transporter [Homo sapiens] >pir S13427 A41538 ATP-binding cassette transporter TAP1 - human >gi 34636 ABC- transporter [Homo sapiens] {SUB 61-808} >gi 930122 Y3 gene product [Homo sapiens] {SUB 183-612} Length = 808 | gi 36061 | 100 | 2169 | 90 | 90 | HNFDY03 |
| 309 | 839611 | | | 548 | 793 | | | HAMFI54 |
| 310 | 840138 | start position 1 [Homo sapiens] >sp E1335356 E1335356 ASMTL PROTEIN. >gnl PI D e1335357 start position 2 [Homo sapiens] {SUB 59-629} Length = 629 | gnl PI D e1335 356 | 1 | 1800 | 92 | 93 | HFIHW86 |

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|-----|--------|--|----------------------|-----|------|-----|-----|---------|
| 311 | 840616 | Homology with Squid retinal-binding protein (PIR Acc. No. A53057) [Caenorhabditis elegans] >sp Q22467 Q22467.T13H5.2 PROTEIN. Length = 1254 | gnl PID e 349 397 | 3 | 1607 | 73 | 86 | HMSCY51 |
| 312 | 840780 | unknown [Saccharomyces cerevisiae] >pir S58704 S58704 probable membrane protein YIL003w - yeast (Saccharomyces cerevisiae) >gil 558401 incomplete orf, len: 160, CAI: 0.09 similar to MRP_ECOLI P21590 39.9 KD PROTEIN [Saccharomyces cerevisiae] {SUB 1-158} >g | gil 763343 | 17 | 880 | 57 | 80 | HGEDY61 |
| 313 | 840857 | (AF071059) zinc finger RNA binding protein [Mus musculus] >sp O88532 O88532 ZINC FINGER RNA BINDING PROTEIN. Length = 1052 cysteine-rich intestinal protein [Homo sapiens] >pir G02666 G02666 cysteine-rich protein l - human Length = 77 | gil 3293537 | 459 | 2669 | 94 | 94 | HLHDQ83 |
| 314 | 840862 | | gil 1381638 | 36 | 353 | 100 | 100 | HEPAP58 |
| 315 | 840864 | | | 407 | 1096 | | | HTLHY48 |
| 316 | 840936 | homologous to Swiss-Prot accession number P16371 [Homo sapiens] >gil 3850562 (AC005944) GRG_HUMAN; ESPI PROTEIN; AMINO ENHANCER OF SPLIT; AES-1/AES-2; gp130 associated protein GAM [Homo sapiens] >pir G01236 G01236 enhancer of split m9/m10 (groucho protein) | gil 435425 | 3 | 668 | 79 | 79 | HOENU32 |

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|-----|--------|---|----------------------|-----|------|----|----|----------|
| 317 | 840938 | carbonyl reductase [Sus scrofa] >pir JN0703 JN0703 carbonyl reductase (NADPH) (EC 1.1.1.184) - pig >sp Q29529 CBR2_PIG LUNG CARBONYL REDUCTASE [NADPH] (EC 1.1.1.184) (NADPH-DEPENDENT CARBONYL REDUCTASE) (LCR). Length = 244 | gnl PID d100 4479 | 2 | 745 | 65 | 76 | HMCA175 |
| 318 | 841884 | | | 677 | 1324 | | | HLQB145 |
| 319 | 842241 | (AJ009698) embigin protein [Rattus norvegicus] >sp O88775 O88775 EMBIGIN PROTEIN PRECURSOR. Length = 328 | gnl PID e1312 986 | 2 | 952 | 60 | 75 | HOFMD52 |
| 320 | 843712 | | | 2 | 202 | | | HSSGR77 |
| 321 | 844040 | ribosomal protein L11 [Caenorhabditis elegans] >pir S27795 S27795 ribosomal protein L11 homolog - Caenorhabditis elegans Length = 195 | gil156201 | 75 | 500 | 42 | 64 | HIPTGB84 |
| 322 | 844336 | (AB009462) LDL receptor related protein 105 [Homo sapiens] >sp O75074 O75074 LDL RECEPTOR RELATED PROTEIN 105. Length = 770 | gnl PID d103 3292 | 831 | 2285 | 68 | 75 | HWMFE21 |
| 323 | 844612 | collagen binding protein 2 [Homo sapiens] >pir 52968 52968 colligin-2 - human >sp P50454 CBP2_HUMAN COLLAGEN- BINDING PROTEIN 2 PRECURSOR (COLLIGIN 2). Length = 418 | gnl PID d101 2496 | 528 | 1466 | 96 | 97 | HOFME75 |
| 324 | 844617 | | | 556 | 735 | | | HMVZ36 |

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|-----|----------|---|------------|-----|------|----|----|-----------|
| 325 | 845251 | LIV-1 protein [Homo sapiens] >pir G02273 G02273 LIV-1 protein - human >sp Q13433 Q13433 ESTROGEN REGULATED LIV-1 PROTEIN. Length = 752 | gi 1256001 | 23 | 634 | 49 | 67 | HBGBB42 |
| 326 | 845764 | | | 2 | 244 | | | HULCF61 |
| 327 | 846187 | ATPase alpha subunit (aa 1-1023) [Homo sapiens] >gn P1D1d1000505 Na,K-ATPase alpha-subunit [Homo sapiens] >pir A24414 A24414 Na+/K+-exchanging ATPase (EC 3.6.1.37) alpha-1 chain - human >sp P05023 A TN1_HUMAN SODIUM/POTASSIUM- TRANSPORTING ATPASE ALPHA-1 C | gi 28927 | 151 | 2403 | 92 | 92 | HIDPLV27 |
| 328 | HBGDH47R | | | 167 | 241 | | | IIBGDI147 |
| 329 | HHENQ86R | | | 2 | 112 | | | HHENQ86 |
| 330 | HBGBH23R | (AE000161) bacteriophage lambda endopeptidase homolog [Escherichia coli] >pir B64788 B64788 bacteriophage lambda endopeptidase homolog (EC 3.4.-.-) - Escherichia coli (strain K-12) >sp P75719 ENPP_ECOLI PUTATIVE ENDOPEPTIDASE (EC 3.4.-.-). Length = 153 | gi 1786769 | 1 | 213 | 92 | 92 | HBGBH23 |
| 331 | HANGA53R | (AF013214) acidic ribosomal phosphoprotein PO [Bos taurus] Length = 302 | gi 2293577 | 76 | 402 | 80 | 84 | HANGA53 |

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| 332 | HBIMC29R | (AF035959) type-2 phosphatidic acid phosphatase-gamma; phosphatidate phosphohydrolase; phospholipid phosphatase [Homo sapiens] >gi 3025880 (AF056083) phosphatidic acid phosphatase type 2 [Homo sapiens] >gi 2911498 (AF047760) phosphatidic acid phosphohydro (AF061340) F1 ATPase subunit 6 [Artibeus jamaicensis] Length = 226 (AF070447) barrier-to-autointegration factor [Homo sapiens] >sp O75531 O75531 BARRIER-TO-AUTOINTEGRATION FACTOR. Length = 89 | gi 3123896 | 3 | 317 | 96 | 96 | HBIMC29 |
| 333 | HOFAB89R | | gi 4164480 | 86 | 268 | 67 | 82 | HOFAB89 |
| 334 | HAHCP93R | | gi 3220255 | 116 | 289 | 69 | 76 | HAHCP93 |
| 335 | HBGAA76R | | | 14 | 232 | | | HBGAA76 |
| 336 | HBGBT12R | A (DNA packaging;641) [Bacteriophage lambda] >pir D04333 VBPAL DNA-packaging protein A - phage lambda Length = 641 | gi 215106 | 2 | 349 | 95 | 95 | HBGBT12 |
| 337 | HBGBH53R | Actin [Drosophila melanogaster] >pir S14851 S14851 actin - fruit fly (Drosophila melanogaster) >sp Q24228 Q24228 ACTIN. Length = 100 | gi 7550 | 2 | 445 | 93 | 97 | HBGBH53 |

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| 338 | HTXPI29R | aldolase A (EC 4.1.3.13) [Homo sapiens] >gil28597 aldolase A (AA 1-364) [Homo sapiens] >pir S14084 ADHUA fructose-bisphosphate aldolase (EC 4.1.2.13) A - human >sp P04075 ALFA_HUMAN FRUCTOSE-BISPHOSPHATE ALDOLASE A (EC 4.1.2.13) (MUSCLE-TYPE ALDOLASE). {S | gil178351 | 1 | 453 | 86 | 86 | HTXPI29 |
| 339 | HOFMG33R | ATPase [Equus caballus] >sp P48662 ATP6_HORSE ATP SYNTHASE A CHAIN (EC 3.6.1.34) (PROTEIN 6). Length = 226 | gil577577 | 28 | 309 | 57 | 62 | HOFMG33 |
| 340 | HCGAC11R | | | 1 | 345 | | | HCGAC11 |
| 341 | HCIAC54R | | | 37 | 168 | | | HCIAC54 |
| 342 | HBGAA54R | | | 1 | 282 | | | HBGAA54 |
| 343 | HAOMC34R | calpactin I heavy chain (p36) [Bos taurus] >pir A03081 LUBO36 annexin II - bovine >sp P04272 ANX2_BOVIN ANNEXIN II (LIPOCORTIN II) (CALPACTIN I HEAVY CHAIN) (CHROMOBINDIN 8) (P36) (PROTEIN I) (PLACENTAL ANTICOAGULANT PROTEIN IV) (PAP-IV). {SUB 2-339} Leng >sp Q99829 Q99829 COPINE I. Length = 537 | gil162779 | 2 | 115 | 73 | 80 | HAOMC34 |
| 344 | H2LAU88R | copine I [Homo sapiens] >sp Q99829 Q99829 COPINE I. Length = 537 | gil1791257 | 1 | 576 | 95 | 95 | H2LAU88 |
| 345 | HDPJR77R | DNA topoisomerase II [Homo sapiens] >gil38325 DNA topoisomerase II [Homo sapiens] {SUB 448-681} Length = 1031 | gil288565 | 3 | 311 | 100 | 100 | HDPJR77 |

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|-----|----------|---|-----------------|----|-----|-----|-----|---------|
| 346 | HTTIO41R | docking protein [Homo sapiens] >pir A29440 A29440 signal recognition particle receptor - human Length = 638 | gj 30866 | 90 | 404 | 94 | 95 | HTTIO41 |
| 347 | H2CBU29R | electron transport flavoprotein [Homo sapiens] >pir A31998 A31998 electron transfer flavoprotein alpha chain precursor - human >sp P13804 ETFA_HUMAN ELECTRON TRANSFER FLAVOPROTEIN ALPHA-SUBUNIT PRECURSOR (ALPHA-ETF) >gn P1D1e1331769 (AJ224002) electron | gj 182251 | 2 | 442 | 100 | 100 | H2CBU29 |
| 348 | HBMVA11R | GARS protein [Homo sapiens] >sp Q15374 Q15374 GARS PROTEIN. Length = 433 | gn P1D1d1007383 | 1 | 108 | 81 | 84 | HBMVA11 |
| 349 | HDPUL86R | GC kinase [Homo sapiens] >pir A53714 A53714 protein kinase (EC 2.7.1.37) BL44 - human >sp Q12851 Q12851 GC KINASE. Length = 819 | gj 531820 | 3 | 317 | 64 | 65 | HDPUL86 |
| 350 | HTXNT16R | GTP-binding protein [Homo sapiens] >gj 577779 GTP-binding protein [Homo sapiens] >pir A55014 A55014 GTP-binding protein - human >sp P55039 DRG2_HUMAN DEVELOPMENTALLY REGULATED GTP-BINDING PROTEIN DRG2. Length = 364 | gj 577779 | 2 | 463 | 100 | 100 | HTXNT16 |
| 351 | HBGAA13R | H (tail component;853) [Bacteriophage lambda] >pir G43008 TLBPHL minor tail protein precursor H - phage lambda Length = 853 | gj 215120 | 1 | 267 | 97 | 97 | HBGAA13 |

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|-----|-----------|---|------------|-----|-----|----|----|----------|
| 352 | HLXNA54R | heat shock protein HSP27 [Homo sapiens] >gi 433598 28 kDa heat shock protein [Homo sapiens] >gi 1913885 heat shock protein [Homo sapiens] >pir S12102 HHHU27 heat shock protein 27 - human >sp G248440 G248440 28 KDA HEAT SHOCK PROTEIN HOMOLOG FRAGMENT 2. {S Hep27 protein [Homo sapiens] >pir S66665 S66665 nuclear protein Hep27 - human >sp Q13268 HE27_HUMAN HEP27 PROTEIN (PROTEIN D). {SUB 24-280} Length = 280 | gi 32478 | 2 | 256 | 98 | 98 | HLXNA54 |
| 353 | HCHOH37R | Hep27 protein [Homo sapiens] >pir S66665 S66665 nuclear protein Hep27 - human >sp Q13268 HE27_HUMAN HEP27 PROTEIN (PROTEIN D). {SUB 24-280} Length = 280 | gi 1079566 | 337 | 564 | 75 | 81 | HCHOH37 |
| 354 | H2LAX93R | histone H2B [Gallus gallus] >gi 63434 histone H2B [Gallus gallus] >gi 63452 histone H2B (AA 1 - 126) [Gallus gallus] >gi 63456 histone H2B (AA 1 - 126) [Gallus gallus] >gi 63458 histone H2B [Gallus gallus] >gi 63460 histone H2B (AA 1 - 126) [Gallus gallus] homologue to elongation factor 1-gamma from A.salina [Homo sapiens] >gi 31104 elongation factor-1-gamma [Homo sapiens] >pir S22655 S22655 translation elongation factor eEF-1 gamma chain - human >sp P26641 EF1G_HUMAN ELONGATION FACTOR 1-GAMMA (EF- 1-GAMMA). | gi 211845 | 191 | 505 | 89 | 96 | H2LAX93 |
| 355 | HWAFFW10R | homologue to elongation factor 1-gamma from A.salina [Homo sapiens] >gi 31104 elongation factor-1-gamma [Homo sapiens] >pir S22655 S22655 translation elongation factor eEF-1 gamma chain - human >sp P26641 EF1G_HUMAN ELONGATION FACTOR 1-GAMMA (EF- 1-GAMMA). | gi 31102 | 3 | 434 | 98 | 98 | HWAFFW10 |

| | | | | | | | | |
|-----|----------|--|--------------------|---|-----|----|----|---------|
| 356 | HBNAB19R | human complement C1r [Homo sapiens] >pir A24170 C1HURB complement subcomponent C1r (EC 3.4.21.41) precursor - human >sp P00736 C1R_HUMAN COMPLEMENT C1R COMPONENT PRECURSOR (EC 3.4.21.41). Length = 705 | gi 179644 | 2 | 193 | 98 | 98 | HBNAB19 |
| 357 | HBGDD17R | hypothetical protein [Escherichia coli] >gi 1786774 (AE000161) orf, hypothetical protein [Escherichia coli] >pir G64788 G64788 hypothetical protein b0561 - Escherichia coli (strain K-12) Length = 247 | gi 1778474 | 1 | 207 | 98 | 98 | HBGDD17 |
| 358 | HBIAB72R | hypoxanthine phosphoribosyltransferase [Sus scrofa] >sp P79306 P79306 HYPOXANTHINE PHOSPHORIBOSYLTRANSFERASE (FRAGMENT). Length = 85 | gn P D e2919 69 | 2 | 169 | 81 | 86 | HBIAB72 |
| 359 | HFIEH41R | interferon-gamma induced protein [Homo sapiens] >pir I54501 I54501 interferon gamma-induced protein IFI 16 - human >sp Q16666 IFI16_HUMAN GAMMA- INTERFERON-INDUCIBLE PROTEIN IFI-16 (INTERFERON-INDUCIBLE MYELOID DIFFERENTIATION TRANSCRIPTIONAL ACTIVATOR). Le | gi 184569 | 5 | 406 | 96 | 97 | HFIEH41 |
| 360 | H2CBB43R | J (tail:host specificity;1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132 | gi 215125 | 2 | 400 | 99 | 99 | H2CBB43 |

| | | | | | | | |
|-----|----------|--|---|-----|-----|-----|---------|
| 361 | H2CBQ77R | J (tail:host specificity;1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132 | 3 | 272 | 97 | 97 | H2CBQ77 |
| 362 | HATAO24R | J (tail:host specificity;1132) [Bacteriophage lambda] >pir D43009 QSBPL host specificity protein J - phage lambda Length = 1132 | 2 | 247 | 71 | 71 | HATAO24 |
| 363 | HOEMK06R | K (tail component;199) [Bacteriophage lambda] >pir H43009 TJBPKL tail assembly protein K - phage lambda Length = 199 | 3 | 149 | 97 | 97 | HOEMK06 |
| 364 | HADCH03R | mitochondrial acetoacetyl-CoA thiolase precursor [Homo sapiens] Length = 427 | 2 | 256 | 83 | 83 | HADCH03 |
| 365 | HCHAG30R | Mta1 [Rattus norvegicus] >pir A54766 A54766 metastasis-associated protein mta-1 - rat >sp Q62599 MTA1_RAT METASTASIS-ASSOCIATED PROTEIN MTA1. Length = 703 | 2 | 271 | 92 | 92 | HCHAG30 |
| 366 | HOFAD96R | NADH dehydrogenase subunit 4L [Felis catus] >sp P4893 INULM_FELCA NADH-UBIQUINONE OXIDOREDUCTASE CHAIN 4L (EC 1.6.5.3). Length = 98 | 2 | 253 | 50 | 52 | HOFAD96 |
| 367 | H2CBX07R | Nin 221 (pept unknown;221) [Bacteriophage lambda] >pir G4301 Q1BP1L multiple specificity phosphoprotein phosphatase (EC 3.1.3.-) - phage lambda >sp P03772 PP_LAMBD SERINE/THREONINE PROTEIN PHOSPHATASE (EC 3.1.3.16). Length = 221 | 2 | 184 | 100 | 100 | H2CBX07 |

| | | | | | | | | |
|-----|----------|---|----------------------|-----|-----|----|-----|---------|
| 368 | HDPLN02R | nuclear corepressor KAP-1 [Homo sapiens] Length = 835 | gij1699027 | 149 | 454 | 90 | 90 | HDPLN02 |
| 369 | HT4FU27R | nuclear corepressor KAP-1 [Homo sapiens] Length = 835 | gij1699027 | 96 | 287 | 95 | 95 | HT4FU27 |
| 370 | HAELI26R | open reading frame A; putative [Homo sapiens] Length = 84 | gij190369 | 109 | 291 | 78 | 80 | HAELI26 |
| 371 | HCDAR56R | p23 [Homo sapiens] >pir A56211 A56211 progesterone receptor-related protein p23 - human >sp Q15185 Q15185 (P23). Length = 160 | gij438652 | 2 | 208 | 90 | 92 | HCDAR56 |
| 372 | HCDCW35R | precursor [Homo sapiens] Length = 631 | gij36049 | 3 | 155 | 78 | 84 | HCDCW35 |
| 373 | H2CBN76R | proteasome subunit C5 [Homo sapiens] >gnl PID e1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir S15973 SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp P20618 PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4 | gnl PID d100 1116 | 3 | 464 | 99 | 99 | H2CBN76 |
| 374 | HAGFX49R | proteasome subunit C5 [Homo sapiens] >gnl PID e1334433 (AL031259) C5 (proteasome subunit HC5) [Homo sapiens] >pir S15973 SNHUC5 multicatalytic endopeptidase complex (EC 3.4.99.46) chain C5 - human >sp P20618 PRC5_HUMAN PROTEASOME COMPONENT C5 (EC 3.4.99.4 | gnl PID d100 1116 | 1 | 288 | 98 | 100 | HAGFX49 |

| | | | | | | | | |
|-----|-----------|---|-----------------|----|-----|-----|-----|----------|
| 375 | HNEEG64R | put. major coat protein (AA 1-341) [Bacteriophage phi-80] >pir S03314 VHBP80 major capsid protein - phage phi-80 >sp P05481 HEAD_BPPH8 MAJOR HEAD PROTEIN (GPE) (GP5) (MAJOR COAT PROTEIN). Length = 341 | gil 15769 | 17 | 232 | 81 | 97 | HNEEG64 |
| 376 | HTXKR32R | putative nucleotide-binding protein [Homo sapiens] >pir JC4010 JC4010 nucleotide-binding protein - human >sp P53384 NBP_HUMAN NUCLEOTIDE-BINDING PROTEIN (NBP). Length = 320 | gil 15644 | 3 | 374 | 100 | 100 | HTXKR32 |
| 377 | HAIBZ58R | putative start codon [Homo sapiens] Length = 210 | gil 895845 | 2 | 433 | 65 | 65 | HAIBZ58 |
| 378 | H6EAF46R | rexa (exclusion;279) [Bacteriophage lambda] >gil 15068 reading frame (rex1 protein) [Bacteriophage 434] >pir E43010 IMBPAL rexA protein - phage lambda Length = 279 | gil 215146 | 43 | 333 | 92 | 93 | H6EAF46 |
| 379 | H2LA W60R | ribosomal protein L27a [Homo sapiens] >pir S55914 S55914 ribosomal protein L27a - human Length = 148 | gil 550017 | 3 | 545 | 88 | 88 | H2LA W60 |
| 380 | H2LAK40R | ribosomal protein L31 [Sus scrofa] >gil 36130 ribosomal protein L31 (AA 1-125) [Homo sapiens] >gil 57115 ribosomal protein L31 (AA 1-125) [Rattus norvegicus] >pir S05576 R5HU31 ribosomal protein L31 - human >pir A26417 R5RT31 ribosomal protein L31 - rat >gn | gnl PID e276436 | 76 | 483 | 77 | 80 | H2LAK40 |

| | | | | | | | | |
|-----|----------|---|------------|-----|-----|-----|-----|---------|
| 381 | H2LAY71R | ribosomal protein L35 [Homo sapiens] >pir G01477 G01477 ribosomal protein L35 - human Length = 123 | gi 562074 | 70 | 495 | 100 | 100 | H2LAY71 |
| 382 | HCHAH62R | ribosomal protein L8 [Homo sapiens] >gi 57704 ribosomal protein L8 [Rattus rattus] >gi 1527178 ribosomal protein L8 [Mus musculus] >pir J00177 RSRTL8 ribosomal protein L8, cytosolic - rat >pir JN0923 JN0923 ribosomal protein L8, cytosolic - human >gi 3851 | gi 433899 | 1 | 222 | 76 | 76 | HCHAH62 |
| 383 | H6EEF31R | ribosomal protein S2 [Rattus norvegicus] >sp O5521 O55211 RIBOSOMAL PROTEIN S2. Length = 257 | gi 2920825 | 1 | 300 | 89 | 91 | H6EEF31 |
| 384 | HDPBT55R | RNAse L inhibitor [Mus musculus] >sp O88793 O88793 RNAse L INHIBITOR. Length = 599 | gi 3273417 | 71 | 127 | 81 | 86 | HDPBT55 |
| 385 | HASAW80R | S.macroura Wilms tumour protein [Sminthopsis macroura] Length = 239 | gi 987118 | 1 | 162 | 90 | 98 | HASAW80 |
| 386 | HCHAF25R | SSR alpha subunit [Homo sapiens] >pir 38246 38246 SSR alpha subunit - human Length = 286 | gi 551638 | 2 | 421 | 95 | 95 | HCHAF25 |
| 387 | HLTHH84R | UMP synthase [Homo sapiens] >pir A30148 A30148 UMP synthase - human Length = 480 | gi 340168 | 2 | 391 | 99 | 99 | HLTHH84 |
| 388 | H2CBU20R | | | 39- | 143 | | | H2CBU20 |
| 389 | HADAA62R | | | 3 | 218 | | | HADAA62 |
| 390 | HADDC09R | | | 16 | 174 | | | HADDC09 |
| 391 | HAIAB75R | | | 2 | 211 | | | HAIAB75 |

| | | | | |
|-----|----------|-----|-----|---------|
| 392 | HAMGA37R | 3 | 119 | HAMGA37 |
| 393 | HAQA110R | 1 | 81 | HAQA110 |
| 394 | HBFME95R | 3 | 218 | HBFME95 |
| 395 | HBGBH24R | 1 | 81 | HBGBH24 |
| 396 | HBGBT78R | 1 | 69 | HBGBT78 |
| 397 | HGCB06R | 3 | 140 | HGCB06 |
| 398 | HGDO01R | 1 | 156 | HGDO01 |
| 399 | HBIBJ73R | 3 | 341 | HBIBJ73 |
| 400 | HBJLE85R | 3 | 398 | HBJLE85 |
| 401 | HBNAD53R | 2 | 187 | HBNAD53 |
| 402 | HBNAT63R | 54 | 173 | HBNAT63 |
| 403 | HCE4H65R | 2 | 193 | HCE4H65 |
| 404 | HCFLJ44R | 92 | 274 | HCFLJ44 |
| 405 | HCHMW05R | 3 | 221 | HCHMW05 |
| 406 | HCHNR50R | 2 | 103 | HCHNR50 |
| 407 | HE8DS01R | 2 | 64 | HE8DS01 |
| 408 | HFEBP31R | 109 | 276 | HFEBP31 |

| | | | | |
|-----|----------|-----|-----|---------|
| 409 | HLDXE36R | 6 | 167 | HLDXE36 |
| 410 | HLTGV28R | 181 | 414 | HLTGV28 |
| 411 | HODFW25R | 42 | 308 | HODFW25 |
| 412 | HOEMQ91R | 1 | 129 | HOEMQ91 |
| 413 | HOGBG56R | 57 | 386 | HOGBG56 |
| 414 | HOSMT44R | 2 | 151 | HOSMT44 |
| 415 | HRAEE04R | 51 | 191 | HRAEE04 |
| 416 | HULFN65R | 3 | 272 | HULFN65 |
| 417 | HWLVW23R | 1 | 153 | HWLVW23 |
| 418 | HWLWE77R | 149 | 289 | HWLWE77 |

The first column of Table 1 shows the "SEQ ID NO:" for each of the 418 breast/ovarian cancer antigen polynucleotide sequences of the invention.

The second column in Table 1, provides a unique "Sequence/Contig ID" identification for each breast, ovarian, breast cancer and/or ovarian cancer associated sequence. The third column in Table 1, "Gene Name," provides a putative identification of the gene based on the sequence similarity of its translation product to an amino acid sequence found in a publicly accessible gene database, such as GenBank (NCBI). The great majority of the cDNA sequences reported in Table 1 are unrelated to any sequences previously described in the literature. The fourth column, in Table 1, "Overlap," provides the database accession no. for the database sequence having similarity. The fifth and sixth columns in Table 1 provide the location (nucleotide position nos. within the contig), "Start" and "End", in the polynucleotide sequence "SEQ ID NO:X" that delineate the preferred ORF shown in the sequence listing as SEQ ID NO:Y. In one embodiment, the invention provides a protein comprising, or alternatively consisting of, a polypeptide encoded by the portion of SEQ ID NO:X delineated by the nucleotide position nos. "Start" and "End". Also provided are polynucleotides encoding such proteins and the complementary strand thereto. The seventh and eighth columns provide the "% Identity" (percent identity) and "% Similarity" (percent similarity) observed between the aligned sequence segments of the translation product of SEQ ID NO:X and the database sequence.

The ninth column of Table 1 provides a unique "Clone ID" for a clone related to each contig sequence. This clone ID references the cDNA clone which contains at least the 5' most sequence of the assembled contig and at least a portion of SEQ ID NO:X was determined by directly sequencing the referenced clone. The reference clone may have more sequence than described in the sequence listing or the clone may have less. In the vast majority of cases, however, the clone is believed to encode a full-length polypeptide. In the case where a clone is not full-length, a full-length cDNA can be obtained by methods described elsewhere herein.

Table 3 indicates public ESTs, of which at least one, two, three, four, five, ten, or more of any one or more of these public ESTs are optionally excluded from the invention.

SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing as SEQ ID NO:1 through SEQ ID NO:418) and the translated SEQ ID NO:Y (where Y may be any of the polypeptide sequences disclosed in the sequence listing as SEQ

ID NO:418 through SEQ ID NO:836) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X has uses including, but not limited to, in designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the related cDNA clone
5 contained in a library deposited with the ATCC. These probes will also hybridize to nucleic acid molecules in biological samples; thereby enabling immediate applications in chromosome mapping, linkage analysis, tissue identification and/or typing, and a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y have uses that include, but are not limited to, generating antibodies which
10 bind specifically to the breast/ovarian cancer antigen polypeptides, or fragments thereof, and/or to the breast/ovarian cancer antigen polypeptides encoded by the cDNA clones identified in Table 1.

Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions
15 of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over
20 1000 bases).

Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X, the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing the related cDNA clone
25 (deposited with the ATCC, as set forth in Table 1). The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. Further, techniques known in the art can be used to verify the nucleotide sequences of SEQ ID NO:X.

The predicted amino acid sequence can then be verified from such deposits.
30 Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

The present invention also relates to vectors or plasmids which include such DNA sequences, as well as the use of the DNA sequences. The material deposited with the ATCC on:

5 Table 2

| ATCC Deposits | Deposit Date | ATCC Designation Number |
|---|--------------|--|
| LP01, LP02, LP03, LP04, LP05, LP06, LP07, LP08, LP09, LP10, LP11, | May-20-97 | 209059, 209060, 209061, 209062, 209063, 209064, 209065, 209066, 209067, 209068, 209069 |
| LP12 | Jan-12-98 | 209579 |
| LP13 | Jan-12-98 | 209578 |
| LP14 | Jul-16-98 | 203067 |
| LP15 | Jul-16-98 | 203068 |
| LP16 | Feb-1-99 | 203609 |
| LP17 | Feb-1-99 | 203610 |
| LP20 | Nov-17-98 | 203485 |
| LP21 | Jun-18-99 | PTA-252 |
| LP22 | Jun-18-99 | PTA-253 |
| LP23 | Dec-22-99 | PTA-1081 |

each is a mixture of cDNA clones derived from a variety of human tissue and cloned in either a plasmid vector or a phage vector, as shown in Table 5. These deposits are referred to as
10 "the deposits" herein. The tissues from which the clones were derived are listed in Table 5, and the vector in which the cDNA is contained is also indicated in Table 5. The deposited material includes the cDNA clones which were partially sequenced and are related to the SEQ ID NO:X described in Table 1 (column 9). Thus, a clone which is isolatable from the
15 ATCC Deposits by use of a sequence listed as SEQ ID NO:X may include the entire coding region of a human gene or in other cases such clone may include a substantial portion of the coding region of a human gene. Although the sequence listing lists only a portion of the DNA sequence in a clone included in the ATCC Deposits, it is well within the ability of one skilled in the art to complete the sequence of the DNA included in a clone isolatable from the

ATCC Deposits by use of a sequence (or portion thereof) listed in Table 1 by procedures hereinafter further described, and others apparent to those skilled in the art.

Also provided in Table 5 is the name of the vector which contains the cDNA clone. Each vector is routinely used in the art. The following additional information is provided for convenience.

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., *Nucleic Acids Res.* 16:7583-7600 (1988); Altling-Mees, M. A. and Short, J. M., *Nucleic Acids Res.* 17:9494 (1989)) and pBK (Altling-Mees, M. A. et al., *Strategies* 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Phagemid pBS may be excised from the Lambda Zap and Uni-Zap XR vectors, and phagemid pBK may be excised from the Zap Express vector. Both phagemids may be transformed into *E. coli* strain XL-1 Blue, also available from Stratagene.

Vectors pSport1, pCMVSPORT 1.0, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, also available from Life Technologies. See, for instance, Gruber, C. E., et al., *Focus* 15:59 (1993). Vector lacmid BA (Bento Soares, Columbia University, New York, NY) contains an ampicillin resistance gene and can be transformed into *E. coli* strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into *E. coli* strain DH10B, available from Life Technologies. See, for instance, Clark, J. M., *Nuc. Acids Res.* 16:9677-9686 (1988) and Mead, D. et al., *Bio/Technology* 9: (1991).

The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in a deposited cDNA clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include, but are not limited to, preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, and/or the cDNA contained in the related cDNA clone in the deposit, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or the related cDNA clone (See, e.g., columns 1 and 9 of Table 1). The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of, the polypeptide sequence of SEQ ID NO:Y, a polypeptide encoded by SEQ ID NO:X, and/or a polypeptide encoded by the the dDNA in the related cDNA clone contained in a deposited library, are also encompassed by the invention. The present invention further encompasses a polynucleotide comprising, or alternatively consisting of, the complement of the nucleic acid sequence of SEQ ID NO:X, and/or the complement of the coding strand of the related cDNA clone contained in a deposited library.

Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would unduly burden the disclosure of this application. Accordingly, for each "Contig Id" listed in the first column of Table 3, preferably excluded are one or more polynucleotides comprising a nucleotide sequence described in the second column of Table 3 by the general formula of a-b, each of which are uniquely defined for the SEQ ID NO:X corresponding to that Contig Id in Table 1. Additionally, specific embodiments are directed to polynucleotide sequences excluding at least one, two, three, four, five, ten, or more of the specific polynucleotide sequences referenced by the Genbank Accession No. for each Contig Id which may be

included in column 3 of Table 3. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example.

Table 3

| Sequence/ Contig ID | General formula | Genbank Accession No. |
|------------------------|--|--|
| 419266 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1899 of SEQ ID NO:1, b is an integer of 15 to 1913, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:1, and where b is greater than or equal to a + 14. | T68585, T68665, T86313, T86314, R12356, R31374, R32873, R37282, R84617, R85369, R99171, H48474, N23871, N58201, N74557, W90334, AA031318, AA031427, AA130231, AA256587 |
| 429114 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:2, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:2, and where b is greater than or equal to a + 14. | R20542, R42676, R42676, R20542, R61501, H08662, H77556, H97365, N24198, N33135, N74546, N93573, W02941, W52194, AA004624, AA004721, AA046710, AA235395, AA235479 |
| 506777 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 340 of SEQ ID NO:3, b is an integer of 15 to 354, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:3, and where b is greater than or equal to a + 14. | |
| 508678 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 500 of SEQ ID NO:4, b is an integer of 15 to 514, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:4, and where b is greater than or equal to a + 14. | W37175, AA121532, AA127694 |
| 508968 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general | T71941, T94428, T94514, H02313, N26913, N47870, N66244, N92418, W31301, W42459, W42564, AA084031, AA126786, AA258050, AA459772 |

| | | |
|--------|--|--|
| | formula of a-b, where a is any integer between 1 to 2021 of SEQ ID NO:5, b is an integer of 15 to 2035, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:5, and where b is greater than or equal to a + 14. | |
| 509029 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1182 of SEQ ID NO:6, b is an integer of 15 to 1196, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:6, and where b is greater than or equal to a + 14. | R11213, R11271, H14072, H14071, H51531, H66637, H66636, W23707, W35307, AA025586, AA025710, AA058796, AA113917 |
| 519726 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 610 of SEQ ID NO:7, b is an integer of 15 to 624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:7, and where b is greater than or equal to a + 14. | AA236015, AA236085, AA256106 |
| 522632 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 287 of SEQ ID NO:8, b is an integer of 15 to 301, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:8, and where b is greater than or equal to a + 14. | |
| 524655 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 672 of SEQ ID NO:9, b is an integer of 15 to 686, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:9, and where b is greater than or equal to a + 14. | T66495, R15869, R39696, H16266, H20784, H22599, N68150, W58001, W57856 |
| 525847 | Preferably excluded from the present | |

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| | invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:10, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:10, and where b is greater than or equal to a + 14. | |
| 530306 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 549 of SEQ ID NO:11, b is an integer of 15 to 563, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14. | |
| 532818 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 429 of SEQ ID NO:12, b is an integer of 15 to 443, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14. | AA188990, AA191040 |
| 533385 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2424 of SEQ ID NO:13, b is an integer of 15 to 2438, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14. | |
| 533532 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2333 of SEQ ID NO:14, b is an integer of 15 to 2347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID | T94240, T77619, R13236, R17515, R33142, R33294, R39249, R40318, R42609, R42609, R40318, R75952, H03594, H12337, H12391, H70913, H70916, H70996, H71001, H87858, H70913, N21374, N31326, N35068, N35435, N43807, N45045, W46431, W46486, W51917, AA019546, AA018858, AA056764, AA056767, AA058441, AA058445, AA083228, AA083269, AA115939, AA122236, AA147307, AA159802, |

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| | NO:14, and where b is greater than or equal to a + 14. | AA165015, AA165642, AA181869, AA186834, AA252269, AA255892, AA463239, AA463240 |
| 534852 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1992 of SEQ ID NO:15, b is an integer of 15 to 2006, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14. | T55469, T63434, R10603, R10604, H50597, H92640, H94634, W39162, W93243, W94634, W94719, N90240, AA053667, AA167312, AA253414, AA253389 |
| 537910 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 972 of SEQ ID NO:16, b is an integer of 15 to 986, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14. | R23785 |
| 538460 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1575 of SEQ ID NO:17, b is an integer of 15 to 1589, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14. | R13084, R40514, R40514, R55303, R55402, W67446 |
| 539577 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 832 of SEQ ID NO:18, b is an integer of 15 to 846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14. | T49208, N35488, AA088419, AA127572, AA127649, AA156316, AA169250 |
| 548379 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2178 of SEQ ID NO:19, b | R23778, H70824 |

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| | is an integer of 15 to 2192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14. | |
| 548489 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 997 of SEQ ID NO:20, b is an integer of 15 to 1011, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14. | T49861, T49862, T56225, T56367, T72170, T72948, T92867, T74728, R08625, R08719, R17408, R24674, R25174, R25378, R25997, R26800, R28401, R31330, R31589, R42642, R45259, R42642, R45259, R62552, R62553, R66386, R67726, R68781, R68878, H25120, H25121, H41115, H41190, H41191, R84227, R87629, H53386, H64419, H64476, H72640, H72641, H64419, H99301, N22341, N25846, N29370, N29843, N47918, N57261, N59763, N63813, N94171, W23786, W45524, W72111, W77797, AA010718, AA011164, AA033553, AA033554, AA062727, AA062741, AA062784, AA069811, AA075470, AA075471, AA081844, AA083492, AA084442, AA100358, AA126263, AA126354, AA136544, AA136648, AA146862, AA146863, AA179509, AA179540, AA179775, AA180492, AA181719, AA188903, AA189140, AA226959, AA227247 |
| 548595 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2005 of SEQ ID NO:21, b is an integer of 15 to 2019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14. | T61537, T69836, R10679, R42501, R46798, R42501, R46798, H05289, H05822, H12239, H16816, H40312, R86905, R86985, N21432, N73268, W73102, N91565, AA033533, AA053026, AA121547, AA127684, AA190356, AA195451, AA226965, AA232522, AA258142 |
| 549337 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2008 of SEQ ID NO:22, b is an integer of 15 to 2022, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14. | |
| 549777 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1112 of SEQ ID NO:23, b | T81557, R27931, R38730, R39493, R39494, R66845, R67942, R69099, R69214, R69613, R69703, R69740, R72430, R72478, R73090, R73091, R73872, R73955, R82662, R82715, H01096, H01097, H72113, N76139, W58493, W72884, W74409, W94644, W92532, |

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| | is an integer of 15 to 1126, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14. | AA022916, AA022917, AA039661, AA039660, AA043439, AA054965, AA152376, AA148360, AA181225, AA188435 |
| 553091 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2584 of SEQ ID NO:24, b is an integer of 15 to 2598, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14. | |
| 553827 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 397 of SEQ ID NO:25, b is an integer of 15 to 411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14. | |
| 556350 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:26, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14. | T70920, R01856, R37402, H21077, H21531, R94734, N29364, N32255, N80553, W07675, W58340, W58661, W67208, W67352, AA039658, AA039659, AA046392, AA055650, AA058365, AA070442, AA088882, AA102056, AA134144, AA165363, AA171617, AA173761, AA173771, AA252260, AA464575, AA464679 |
| 556351 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1889 of SEQ ID NO:27, b is an integer of 15 to 1903, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14. | T70981, R01855, R13494, H21076, H24431, H24460, R94817, N47912, AA040086, AA040133, AA055706, AA056162, AA058484, AA102055, AA102304, AA130304, AA173608, AA195879 |
| 557007 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide | H13846, H13894, H16354, H20742, H20743, R97935, R97936, H87445, N29633, AA015991, AA045671, AA045670, AA099154, AA099252 |

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| | sequence described by the general formula of a-b, where a is any integer between 1 to 1319 of SEQ ID NO:28, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14. | |
| 558140 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1313 of SEQ ID NO:29, b is an integer of 15 to 1327, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14. | T62991, W58535, W58500, AA053629, AA083878, AA112892, AA157250, AA157345, AA194089, AA253436, AA250750 |
| 558456 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 695 of SEQ ID NO:30, b is an integer of 15 to 709, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14. | |
| 558708 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1094 of SEQ ID NO:31, b is an integer of 15 to 1108, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14. | R38385, W24640, W48793, W49619 |
| 574789 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:32, b is an integer of 15 to 526, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14. | N49156 |

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| 578203 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 541 of SEQ ID NO:33, b is an integer of 15 to 555, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14. | AA149853 |
| 585385 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 333 of SEQ ID NO:34, b is an integer of 15 to 347, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14. | |
| 588869 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 736 of SEQ ID NO:35, b is an integer of 15 to 750, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14. | |
| 597076 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:36, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14. | |
| 598656 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1521 of SEQ ID NO:37, b is an integer of 15 to 1535, where both a and b correspond to the positions of | |

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| | nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14. | |
| 611880 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 281 of SEQ ID NO:38, b is an integer of 15 to 295, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14. | |
| 614329 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1286 of SEQ ID NO:39, b is an integer of 15 to 1300, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14. | T49777, T51334, T49778, T66835, T66836, T78401, R33579, R33684, R34361, R34476, R72556, R75702, H01591, H02719, H13232, H13599, H13942, H13943, H63376, H80729, H80730, H89353, H89539, H99395, N26995, N32930, N40116, N42081, N50408, N50460, N63978, N67308, N92847, W46413, AA126994, AA128141, AA146958, AA146957, AA425764 |
| 616066 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 201 of SEQ ID NO:40, b is an integer of 15 to 215, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14. | |
| 620956 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 460 of SEQ ID NO:41, b is an integer of 15 to 474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14. | |
| 621889 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | |

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| | between 1 to 411 of SEQ ID NO:42, b is an integer of 15 to 425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14. | |
| 624017 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1173 of SEQ ID NO:43, b is an integer of 15 to 1187, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14. | T61010, AA071044, AA088260, AA098798, AA102017, AA100707, AA111883, AA113305, AA121495, AA133235, AA131438, AA132011, AA132866, AA143457, AA146581, AA146805, AA146928, AA155613, AA155609, AA158090, AA158263, AA164694, AA165591, AA176429, AA226820 |
| 651784 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:44, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14. | W32583, W68240, W94174, AA251670, AA252011, AA252266, AA425209 |
| 651826 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1485 of SEQ ID NO:45, b is an integer of 15 to 1499, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14. | T47384, T47385, T60137, T60194, T71947, T95050, T95146, R25340, R25476, R26117, R26301, R27566, R27664, R28180, R33393, R35872, R35873, R36483, R48329, R48438, R62139, R62244, R66007, R66008, R66764, R70718, R70719, R73674, R73761, R74132, R76569, R76643, R77265, R77312, R78827, R79686, R79687, R81316, R81751, H00804, H00891, H01415, H01416, H02522, H03673, H13925, H13926, H24743, H26369, H26727, H26728, H27132, H27480, H27663, H28192, H28235, H41929, H41977, H42604, H43209, H43258, H45278, H45348, H53585, H53906, H61785, H61786, H78337, H78338, H87337, H87871, H95183, N27090, N27092, N40499, N40502, N99158, W24165, W60193, AA039817, AA041344, AA074512, AA079058, AA079156, AA079157, AA085829, AA085974, AA100095, AA113304, AA142843, AA149898, AA156331, AA157820, AA157895, AA158552, AA159177, AA176093, AA179607, AA179608, AA176333, AA187637, AA186769, AA188622, AA188742, AA188975 |
| 653282 | Preferably excluded from the present | |

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| | invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 379 of SEQ ID NO:46, b is an integer of 15 to 393, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14. | |
| 657122 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 224 of SEQ ID NO:47, b is an integer of 15 to 238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14. | |
| 661442 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 925 of SEQ ID NO:48, b is an integer of 15 to 939, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14. | R18101, AA424721 |
| 664914 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1757 of SEQ ID NO:49, b is an integer of 15 to 1771, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14. | T86944, T87027, R11421, T81153, T81380, R17243, R17453, R19171, R27826, R27927, R35295, R35940, R41854, R42800, R48191, R48192, R49457, R51209, R52247, R53413, R41854, R42800, R49457, R55257, R55475, R59472, R71390, R81811, R81915, H05137, H07974, H30702, H42552, H57923, H58015, N71127, N74282, N75329, N93224, W01557, W04382, W04780, W23438, W35253, W38865, AA176204, AA194869, AA199875, AA251414 |
| 666654 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 383 of SEQ ID NO:50, b is an integer of 15 to 397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID | |

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| | NO:50, and where b is greater than or equal to a + 14. | |
| 667084 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1621 of SEQ ID NO:51, b is an integer of 15 to 1635, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14. | R71869, R71870, H22387, H27160, H46592, H61204, H62108, N25274, N94410, AA026642, AA069188, AA069189, AA076423, AA076388, AA076533, AA076540, AA122346, AA121039, AA121092, AA133121, AA143471, AA143470, AA143728, AA156363, AA156404, AA158498, AA159190, AA159201, AA159286, AA160335, AA159837, AA159573, AA160367, AA159548, AA160456, AA160697, AA160789, AA179329, AA181540, AA182669, AA186881, AA186887, AA188535, AA188540, AA190669, AA190973, AA191557, AA235457, AA458511, AA418203 |
| 667380 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1766 of SEQ ID NO:52, b is an integer of 15 to 1780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14. | T87574, R10276, R10277, T79847, R49790, R49832, R59538, R59539, R86940, R87067, R87722, R98577, R98578, R99022, R99795, H72692, H93036, H93942, H93941, N54059, N62326, N64719, N66726, N73888, N74171, N91734, N93505, W02054, W03949, W04337, W21317, AA192562, AA192563, AA223984, AA224049 |
| 669530 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:53, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14. | T49160, T49161, H41659, R88196, W60799, W60930, AA046915, AA046972, AA069703, AA464334 |
| 671315 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1930 of SEQ ID NO:54, b is an integer of 15 to 1944, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14. | |
| 671993 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | |

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| | between 1 to 980 of SEQ ID NO:55, b is an integer of 15 to 994, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14. | |
| 674618 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 314 of SEQ ID NO:56, b is an integer of 15 to 328, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14. | |
| 675027 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1475 of SEQ ID NO:57, b is an integer of 15 to 1489, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14. | T86474, AA133454, AA203346 |
| 677202 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1269 of SEQ ID NO:58, b is an integer of 15 to 1283, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14. | T47486, T47487, T47666, T50413, T50493, T50519, T51852, T53234, T57067, T60776, T40856, T93579, T94432, T94435, T96391, R43542, R43542, H21618, H73240, H88867, H88868, H89122, H88868, H89122, N21997, N22243, N22815, N45720, N48998, N52063, N59239, N62103, N66419, N66708, N66782, N67139, N67283, N67447, N68047, N70159, N71198, N74676, N76707, N78333, N80016, N92971, N93518, W05738, W45694, W48845, W80602, AA057801, AA063330, AA064827, AA065165, AA065178, AA065179, AA069552, AA070491, AA070949, AA070969, AA071333, AA071358, AA074331, AA081280, AA111928, AA112051, AA132018, AA132121, AA147357, AA157065, AA157085, AA157890, AA160054, AA181729, AA182765, AA187698, AA186444, AA196168, AA196244, AA224187 |
| 678504 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 726 of SEQ ID NO:59, b is | |

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| | an integer of 15 to 740, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14. | |
| 678985 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1277 of SEQ ID NO:60, b is an integer of 15 to 1291, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14. | |
| 682161 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:61, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14. | |
| 683476 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 604 of SEQ ID NO:62, b is an integer of 15 to 618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14. | |
| 691146 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1124 of SEQ ID NO:63, b is an integer of 15 to 1138, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14. | T48865, T48866, T48901, T47562, T48902, T54258, T54365, T69783, T70768, R08012, R09058, R09059, T83437, T84082, T99021, R09059, R19174, R21551, R22562, R28286, R48757, R48758, R49683, R49683, R62406, R62407, R70222, R75607, R77000, R78400, R78401, R80802, H02840, H03734, H24549, H26291, H26447, H27912, H43630, H47817, R83903, R83904, R94147, H49533, H49773, H50716, H50820, H87446, H87553, H93471, H93472, H98814, N22867, N32137, N32762, N34334, N35009, N36932, N43763, N46205, N52251, N56805, N72290, N95794, W02713, W02886, W17176, W24905, W25571, W25688, |

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| | | W67795, W72687, W72962, W77793, W79704, W81376, W86301, W86316, AA025519, AA025959, AA026653, AA029556, AA029704, AA079472, AA121306, AA136679, AA148681, AA148680, AA181745, AA425923 |
| 693589 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 404 of SEQ ID NO:64, b is an integer of 15 to 418, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14. | |
| 694991 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2822 of SEQ ID NO:65, b is an integer of 15 to 2836, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14. | |
| 698303 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2291 of SEQ ID NO:66, b is an integer of 15 to 2305, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14. | T83582, T84417, T85606, R66380, R67111, R76298, H96019, H96020, N25659, N25661, N34260, N34263, N70618, W05500, W15421, W23670, W39659, AA015855, AA033569, AA033570, AA044566, AA044583, AA178933, AA179025 |
| 698669 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1893 of SEQ ID NO:67, b is an integer of 15 to 1907, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14. | T47115, T47116, R48786, R48893, R55495, R71847, R78934, R79033, R82776, H26587, H27077, R97760, H59232, H79115, H79116, N22948, N23658, N26858, N28757, N39967, N71599, W24648, W60157, W67490, W67491, W67815, W72921, W94215, AA009634, AA026899, AA026900, AA029244, AA029040, AA031846, AA031847, AA032073, AA034285, AA034992, AA036865, AA037006, AA040908, AA039990, AA040521, AA040522, AA040773, AA043726, AA044071, AA044182, AA042948, AA043067, AA046606, AA046721, AA062914, AA074334, AA076039, AA076203, AA079763, AA079764, AA082550, AA085926, AA099318, |

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| | | AA099836, AA102385, AA101039, AA101040, AA112571, AA112572, AA114828, AA114951, AA128001, AA128082, AA126986, AA128134, AA128459, AA129910, AA131403, AA131503, AA147437, AA147438, AA150961, AA151051, AA156785, AA156855, AA157912, AA157913, AA158544, AA158545, AA158554, AA158553, AA211822, AA460840, AA461144 |
| 705696 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 801 of SEQ ID NO:68, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14. | H20141, H20156, H20236, H20250, H49965, H50007, H50487, W92252, AA045116, AA134141, AA142968 |
| 706393 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1136 of SEQ ID NO:69, b is an integer of 15 to 1150, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14. | T48975, T51242, T51357, T59673, T59807, T62725, T62875, T72330, T97577, R01168, R21893, R22365, R35745, R41863, R41863, R63676, R65881, R72862, R73334, R75659, R75767, H02871, H03430, H03512, H14924, H23660, H30020, H30277, H39675, H40069, H40278, H40526, H41667, H41700, H43170, H43670, H45130, H45172, H45173, H45433, H46542, H46952, H46953, H62390, H78695, H78777, H84781, H85405, H92309, N20534, N33402, N38945, N57790, N57945, N59752, W94488, W94489, AA044423, AA043057, AA081370, AA081371, AA099447, AA112623, AA112622, AA143199, AA143214, AA149467, AA149553, AA157049, AA157201, AA157952, AA157953, AA158049, AA158435, AA158837, AA158841, AA161074, AA161078, AA180395, AA251447, AA419021, AA428783, AA429093 |
| 707357 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 330 of SEQ ID NO:70, b is an integer of 15 to 344, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14. | |
| 707360 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general | |

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| | formula of a-b, where a is any integer between 1 to 434 of SEQ ID NO:71, b is an integer of 15 to 448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14. | |
| 707375 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2811 of SEQ ID NO:72, b is an integer of 15 to 2825, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14. | T54138, T65139, T65330, T80324, T83140, R00512, R00612, R19513, R31469, R31470, R47795, R77921, R78022, R80012, H02327, H02429, H06404, H06405, H08607, H08608, H14264, H18370, H19266, H19267, H21399, H21471, H47094, H47185, R85467, R87496, R87501, R87581, R88189, R88226, R88227, N23376, N32357, N58463, N66212, N93661, N99103, W19083, W24383, W68601, W68602, W68723, W68745, AA016149, AA040296, AA056973, AA135439, AA135519, AA135580, AA135856, AA158858, AA161122, AA226730, AA226764, AA227471, AA227481, AA232259 |
| 707754 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 496 of SEQ ID NO:73, b is an integer of 15 to 510, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14. | |
| 711172 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 444 of SEQ ID NO:74, b is an integer of 15 to 458, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14. | |
| 712248 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 363 of SEQ ID NO:75, b is an integer of 15 to 377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or | |

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| | equal to $a + 14$. | |
| 715445 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 2056 of SEQ ID NO:76, b is an integer of 15 to 2070, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to $a + 14$. | T88778, T97557, T97604, R17189, R27615, R30849, R41740, R48616, R41740, H12351, R93768, R98882, R98972, H59983, N23156, N32736, N34539, N55086, N62785, N67224, N77297, N78823, N79734, W07252, W90651, AA037793, AA037794, AA055196, AA055286, AA113425, AA233917, AA234165, AA258602, AA258548, AA426581, AA429080 |
| 716362 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 983 of SEQ ID NO:77, b is an integer of 15 to 997, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to $a + 14$. | |
| 716835 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1319 of SEQ ID NO:78, b is an integer of 15 to 1333, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to $a + 14$. | |
| 716947 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 546 of SEQ ID NO:79, b is an integer of 15 to 560, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to $a + 14$. | |
| 717685 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 3189 of SEQ ID NO:80, b is an integer of 15 to 3203, where both a | T54040, N35800, W45088, AA122232, AA121109, AA126030, AA126152, AA155618, AA155656 |

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| | and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to $a + 14$. | |
| 719755 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1696 of SEQ ID NO:81, b is an integer of 15 to 1710, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to $a + 14$. | |
| 720389 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1365 of SEQ ID NO:82, b is an integer of 15 to 1379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to $a + 14$. | |
| 720903 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 664 of SEQ ID NO:83, b is an integer of 15 to 678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to $a + 14$. | |
| 721348 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2789 of SEQ ID NO:84, b is an integer of 15 to 2803, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to $a + 14$. | |
| 721562 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general | |

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| | formula of a-b, where a is any integer between 1 to 1264 of SEQ ID NO:85, b is an integer of 15 to 1278, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14. | |
| 722775 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2571 of SEQ ID NO:86, b is an integer of 15 to 2585, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14. | |
| 724463 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 371 of SEQ ID NO:87, b is an integer of 15 to 385, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14. | |
| 727501 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2486 of SEQ ID NO:88, b is an integer of 15 to 2500, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14. | |
| 728418 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:89, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14. | |
| 728920 | Preferably excluded from the present | |

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| | invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:90, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14. | |
| 732958 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 773 of SEQ ID NO:91, b is an integer of 15 to 787, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14. | |
| 733134 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1643 of SEQ ID NO:92, b is an integer of 15 to 1657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14. | T49547, T49558, T49559, T49560, T49561, T49649, T49650, T70062, T70129, T75532, T95137, R17573, T27052, R19790, R42912, R52618, R53272, R42912, R59922, R59923, R65930, H08841, H08925, H47546, H47547, H47774, H47784, H48119, H64949, H64950, H69959, H69960, H80517, H80569, H81281, H81337, H87618, H87619, H88959, H89042, H95657, H95712, H95729, H88959, H98860, N20108, N23582, N27446, N34733, N49675, N51841, N75517, N78965, N93975, W05310, W17334, W40344, W52084, W52929, W72818, W72819, W86046, W92307, W92294, AA009783, AA009892, AA022930, AA022980, AA024699, AA024734, AA037408, AA045887, AA045888, AA062821, AA081026, AA082088, AA082420, AA102801, AA199861, AA199931, AA220961, AA223217, AA223456, AA224153, AA224177, AA224137, AA224138, AA224341, AA232349, AA232533, AA232117, AA458900, AA459095, AA463299 |
| 734099 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 471 of SEQ ID NO:93, b is an integer of 15 to 485, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or | R22895, H87448 |

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| | equal to $a + 14$. | |
| 734599 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 750 of SEQ ID NO:94, b is an integer of 15 to 764, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to $a + 14$. | |
| 736019 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 693 of SEQ ID NO:95, b is an integer of 15 to 707, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to $a + 14$. | T41219, T50359, T56829, T58426, T58458, T60928, T60984, T64158, T64287, R27157, H03484, H03579, H22546, H22547, H28310, H44067, H44146, R83796, H48481, H48645, H57243, H66162, H66163, H82370, N21110, N21188, N27461, N29155, N29743, N31124, N32398, N39884, N56818, N57165, N57228, N57403, N68904, N73978, N77833, N93027, N93818, N67112, W00894, W00923, W02234, W16676, W21379, W44969, AA064843, AA070697, AA070876, AA071332, AA071265, AA076379, AA076308, AA079524, AA079572, AA081231, AA081401, AA083774, AA083775, AA130308, AA130309, AA132056, AA132160, AA143132, AA146882, AA146883, AA165057, AA164722, AA166939, AA181133, AA187371, AA187804, AA188118, AA186447, AA186448, AA187105, AA187150, AA188273 |
| 738268 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 801 of SEQ ID NO:96, b is an integer of 15 to 815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to $a + 14$. | T48287, T48288, T54477, T54511, R34064, R36907, R49496, R49496, R75625, R75724, H12225, H16384, H19466, H19543, H42166, H42988, H54780, H99297, N22733, N26471, N74933, N93468, W15461, W47542, W47590, N90997, AA010700, AA010701, AA056728, AA088699, AA126219, AA132934, AA156291, AA165516, AA165558, AA176293, AA173448, AA189056, AA233515, AA459831, AA460011 |
| 738911 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 644 of SEQ ID NO:97, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to $a + 14$. | H22593, H52836 |

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| 739226 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 235 of SEQ ID NO:98, b is an integer of 15 to 249, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14. | T57824, N63155, AA027845 |
| 739527 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 738 of SEQ ID NO:99, b is an integer of 15 to 752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14. | |
| 740710 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3045 of SEQ ID NO:100, b is an integer of 15 to 3059, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14. | |
| 742980 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1668 of SEQ ID NO:101, b is an integer of 15 to 1682, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14. | T71993, R12901, R40053, H14591, H14696, R83485, H50584, H50585, H89958, H89966, H89973, H89980, N26005, N34777, N36638, N36637, N44503, N67682, N76121, N79613, W03491, W05571, W31276, W49653, W49727, AA009708, AA009798, AA035612, AA042894, AA043030, AA062953, AA115370, AA133278, AA181268, AA181269, AA193206 |
| 744331 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 924 of SEQ ID NO:102, b is an integer of 15 to 938, where both a and b correspond to the positions of | R25354, R49789, R71735, R71740, H73502, H79224, H87423, H99515, H99516, N24751, N32707, N44511, N52325, N67764, N75095, N93879, W40372, W69127, W69094, W74698, W74736, AA026984, AA035176, AA149088, AA262739, AA464357, AA430724 |

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| | nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14. | |
| 744751 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1998 of SEQ ID NO:103, b is an integer of 15 to 2012, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14. | |
| 745750 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1080 of SEQ ID NO:104, b is an integer of 15 to 1094, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14. | |
| 746285 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2283 of SEQ ID NO:105, b is an integer of 15 to 2297, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14. | T87719, T87928, R99975, R99976, H64714, H65205, H92423, H65205, N47296, N48612, N58085, N58926, N64294, N64508, N72401, N80294, N93405, W04791, W21447, W94582, W95317, AA024856, AA024939, AA037672, AA037673, AA070416, AA075508, AA075507, AA101263, AA148029, AA147953, AA169726, AA171461, AA173095, AA464821 |
| 746416 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 428 of SEQ ID NO:106, b is an integer of 15 to 442, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14. | |
| 747851 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | N44767, W44754 |

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| | between 1 to 1005 of SEQ ID NO:107, b is an integer of 15 to 1019, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to $a + 14$. | |
| 750632 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 697 of SEQ ID NO:108, b is an integer of 15 to 711, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:108, and where b is greater than or equal to $a + 14$. | H48882, W23677, W35110, AA133857 |
| 751315 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:109, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:109, and where b is greater than or equal to $a + 14$. | |
| 754009 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 781 of SEQ ID NO:110, b is an integer of 15 to 795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:110, and where b is greater than or equal to $a + 14$. | |
| 754634 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1318 of SEQ ID NO:111, b is an integer of 15 to 1332, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:111, and where b is greater than or equal to $a + 14$. | N21429 |
| 756637 | Preferably excluded from the present invention are one or more | N44651, W76461 |

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| | polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 729 of SEQ ID NO:112, b is an integer of 15 to 743, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:112, and where b is greater than or equal to a + 14. | |
| 756833 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1676 of SEQ ID NO:113, b is an integer of 15 to 1690, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:113, and where b is greater than or equal to a + 14. | |
| 756878 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 606 of SEQ ID NO:114, b is an integer of 15 to 620, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:114, and where b is greater than or equal to a + 14. | R12122 |
| 757332 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 528 of SEQ ID NO:115, b is an integer of 15 to 542, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:115, and where b is greater than or equal to a + 14. | |
| 760835 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:116, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:116, and where b is greater than or | |

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| | equal to $a + 14$. | |
| 761760 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 714 of SEQ ID NO:117, b is an integer of 15 to 728, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:117, and where b is greater than or equal to $a + 14$. | |
| 762520 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:118, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:118, and where b is greater than or equal to $a + 14$. | T86617, T86618, R47814, R49961, R71921, R71968, H28225, H28275, R94939, R95025, R97173, R97174, R99726, R99904, H52435, H52436, H58879, H58880, H66345, H66395, H80709, H80710, W87663, W87664, AA046620, AA046867, AA055456, AA102380, AA121314, AA150579, AA197300 |
| 764461 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 197 of SEQ ID NO:119, b is an integer of 15 to 211, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:119, and where b is greater than or equal to $a + 14$. | |
| 764517 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1294 of SEQ ID NO:120, b is an integer of 15 to 1308, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:120, and where b is greater than or equal to $a + 14$. | |
| 765132 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2502 of SEQ ID NO:121, b is an integer of 15 to 2516, where both | |

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| | a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:121, and where b is greater than or equal to $a + 14$. | |
| 765667 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1125 of SEQ ID NO:122, b is an integer of 15 to 1139, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:122, and where b is greater than or equal to $a + 14$. | T81691, N27595 |
| 767113 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2100 of SEQ ID NO:123, b is an integer of 15 to 2114, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:123, and where b is greater than or equal to $a + 14$. | |
| 767204 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 569 of SEQ ID NO:124, b is an integer of 15 to 583, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:124, and where b is greater than or equal to $a + 14$. | |
| 767400 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1973 of SEQ ID NO:125, b is an integer of 15 to 1987, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:125, and where b is greater than or equal to $a + 14$. | |
| 767962 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general | T59753, R21255, R21256, R23274, R23364, R71913, R71956, H12633, H12686, H99087, N26954, N33518, N43798, N62998, N66835, N71124, N71156, N74144, N79907, W01554, |

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| | formula of a-b, where a is any integer between 1 to 1437 of SEQ ID NO:126, b is an integer of 15 to 1451, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:126, and where b is greater than or equal to a + 14. | W05537, W19994, W44368, W46357, W46193, W47163, W47284, W52537, W55854, W80804, W80878, W92021, W92022, N90420, AA002178, AA022578, AA022579, AA029899, AA029987, AA034181, AA036856, AA036913, AA043237, AA043566, AA071518, AA082340, AA122159, AA120962, AA146944, AA147449, AA148081, AA151266, AA151267, AA156459 |
| 768040 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1220 of SEQ ID NO:127, b is an integer of 15 to 1234, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:127, and where b is greater than or equal to a + 14. | |
| 769956 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 849 of SEQ ID NO:128, b is an integer of 15 to 863, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:128, and where b is greater than or equal to a + 14. | R68817, R68925, R75906, H14626, H82146, H93109, H93237, N32098, N35721, N45410, N75570, W03043, W04850, AA029607, AA262861, AA463956, AA464092 |
| 770133 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1224 of SEQ ID NO:129, b is an integer of 15 to 1238, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:129, and where b is greater than or equal to a + 14. | |
| 770289 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 365 of SEQ ID NO:130, b is an integer of 15 to 379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:130, and where b is greater than or equal to a + 14. | |

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| 771964 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1772 of SEQ ID NO:131, b is an integer of 15 to 1786, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:131, and where b is greater than or equal to a + 14. | T53984, T55243, T51230, T77632, T91326, T80819, T81219, T84909, T95454, T97320, T99226, T99269, R16575, R16634, R19765, R22987, R23096, R33095, R33188, R37437, R39255, R45185, R45185, R62594, R62642, H03891, H03892, H08679, H08680, H20556, H20650, H46154, H46155, R88298, R90733, R90759, R92224, R92332, R97325, H57663, H58503, H61709, H61913, H62747, H66685, H68924, H68954, H80053, H83342, H95786, H96135, N20464, N20472, N24026, N25491, N35235, N35419, N38769, N44900, N48399, N53146, N55089, N55095, N57767, N58580, N59732, N63942, N70290, N71759, N74938, N77300, N98411, W23555, W52690, W52160, W56557, W56635, W56598, W56594, W73408, W74230, W79843, W93916, AA031492, AA070868, AA071019, AA088788, AA100685, AA112926, AA176829, AA176851, AA193034, AA194065, AA194180, AA194579, AA194703, AA195416, AA195532, AA233792, AA233783, AA233900, AA233920, AA234128, AA234169, AA252704, AA252831, AA416743, AA418391, AA418440 |
| 772582 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 960 of SEQ ID NO:132, b is an integer of 15 to 974, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:132, and where b is greater than or equal to a + 14. | |
| 773387 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 620 of SEQ ID NO:133, b is an integer of 15 to 634, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:133, and where b is greater than or equal to a + 14. | |
| 773827 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1841 of SEQ ID NO:134, | |

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| | b is an integer of 15 to 1855, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:134, and where b is greater than or equal to a + 14. | |
| 774108 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 903 of SEQ ID NO:135, b is an integer of 15 to 917, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:135, and where b is greater than or equal to a + 14. | T96288, R31388, R32886, R63543, R63597, R75811, R75812, H20285, H20509, H20599, H21238, H24872, H29854, H29945, H41103, H41208, H44188, H44189, R85628, R91367, H83459, H83571, H97165, H97164, N25639, N29652, N29777, N32407, N32413, N32580, N32835, N41918, N42281, N56607, N57152, N57196, N69818, N70613, N93340, N93928, N94454, W24358, W25163, W30800, W37904, W37964, W40428, W68631, W68632, W70339, W80994, W81096, W81716, W81253, W81543, W81544, W94206, AA004372, AA011346, AA016002, AA028888, AA029626, AA029627, AA044028, AA044350, AA062804, AA081035, AA131270, AA131354, AA131371 |
| 774636 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1257 of SEQ ID NO:136, b is an integer of 15 to 1271, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:136, and where b is greater than or equal to a + 14. | T54747, T69827, R14146, R50592, R55502, R73615, R73937, H41540, R84981, R85103, R87495, R88553, R88554, R88556, R88818, R88839, R89675, R91235, H51003, H51004, H51581, H79057, N70799, W02680, AA232327, AA232417, AA464467 |
| 775339 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2003 of SEQ ID NO:137, b is an integer of 15 to 2017, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:137, and where b is greater than or equal to a + 14. | |
| 775582 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 923 of SEQ ID NO:138, b is an integer of 15 to 937, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:138, and where b is greater than or | T62486, T62631, H14642, R85991, H73603, N54912, N68727, N80228, N91617, W38518, W67302, W67418, AA171395, AA214500, AA215291, AA464035 |

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| | equal to $a + 14$. | |
| 775779 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2745 of SEQ ID NO:139, b is an integer of 15 to 2759, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:139, and where b is greater than or equal to $a + 14$. | |
| 777809 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1227 of SEQ ID NO:140, b is an integer of 15 to 1241, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:140, and where b is greater than or equal to $a + 14$. | |
| 778927 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3391 of SEQ ID NO:141, b is an integer of 15 to 3405, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:141, and where b is greater than or equal to $a + 14$. | T50777, T50939, R11800, R19713, R31403, R32898, R44269, R44269, R55431, R60041, R60103, R69554, R74340, R74434, H20427, H26615, H26660, H42495, H43482, R85644, H51488, H68618, N58157, N58231, N77611, W39692, W45048, W56828, W57633, AA052900, AA057808, AA074705, AA122120, AA121079, AA121231, AA259051, AA464470 |
| 779262 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2254 of SEQ ID NO:142, b is an integer of 15 to 2268, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:142, and where b is greater than or equal to $a + 14$. | R11844, R71241, R71292, H00159, H88551, H90726, H98059, N28770, N58442, N78033, W32671, AA035075, AA112651, AA112652, AA130035, AA215309, AA251209 |
| 779392 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1743 of SEQ ID NO:143, b is an integer of 15 to 1757, where both | R25284, R36255, R36256, R42970, R46635, R42970, R46635, H28773, N52867, N70541, N77890, W05403, W05783, AA085067, AA085066, AA204650, AA210753, AA211713, AA251462, AA252456, AA460350, AA460780 |

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| | a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:143, and where b is greater than or equal to $a + 14$. | |
| 780149 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1048 of SEQ ID NO:144, b is an integer of 15 to 1062, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:144, and where b is greater than or equal to $a + 14$. | |
| 780583 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1016 of SEQ ID NO:145, b is an integer of 15 to 1030, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:145, and where b is greater than or equal to $a + 14$. | |
| 780960 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 800 of SEQ ID NO:146, b is an integer of 15 to 814, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:146, and where b is greater than or equal to $a + 14$. | |
| 781469 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2664 of SEQ ID NO:147, b is an integer of 15 to 2678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:147, and where b is greater than or equal to $a + 14$. | T95791, H18820, H19074, H22604, H40723, H45802, H46056, H47074, H47156, H86819, H86886, H88675, H88724, H88972, H89058, H88972, N28987, N36053, N39668, N47281, W19145, W68543, W68544, N91577, AA044679, AA044896, AA430011 |
| 781556 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general | T94861, T94906, R21516, R26869, R27098, R36258, R37965, R37966, R78172, H03413, H04116, H14531, H45546, R96826, R98130, N51409, N52365, N64272, N74939, N75136, |

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| | formula of a-b, where a is any integer between 1 to 1014 of SEQ ID NO:148, b is an integer of 15 to 1028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:148, and where b is greater than or equal to a + 14. | W23556, W35208, AA187823, AA191525, AA429367 |
| 781771 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1411 of SEQ ID NO:149, b is an integer of 15 to 1425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:149, and where b is greater than or equal to a + 14. | T95420, T99529, R50341, R52125, R72608, R72630, R72677, R72701, H26733, H26734, H30106, H59788, H82441, N75150, W42750, W42840 |
| 782033 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:150, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:150, and where b is greater than or equal to a + 14. | H53100, H53207, H97410, H98035, N30753, N68541, W42491, W42641, W57808, AA046603, AA046753, AA136886, AA136997, AA143419, AA143420 |
| 782105 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:151, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:151, and where b is greater than or equal to a + 14. | R97486, H72940, W90139 |
| 782122 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1635 of SEQ ID NO:152, b is an integer of 15 to 1649, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:152, and where b is greater than or equal to a + 14. | T54379, T60348, T61029, T54271, T57801, R10793, T78907, T78959, R49078, R55635, R67844, R67845, R69587, R72600, R72666, H04742, H04830, H16978, H24654, H26129, H26308, H26395, H26467, H28100, H28205, H28252, H28895, H28896, H30485, H39554, H42595, H42603, H42662, H43740, H44345, H44346, H44546, H44547, H44960, H45012, H45860, R88120, R88214, H51204, H58080, H58081, H64553, H64654, H70033, H70034, H86451, H70034, H99833, N24525, N29867, N30752, N35500, N39259, N42463, N44804, |

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| | | N52550, N53985, N57289, N58726, N63349, N67624, N67663, N68157, N70299, N80615, N93230, N94595, N98489, W19633, W23803, W25087, W31034, W37981, W37982, W42579, W44389, W49677, W57614, W57871, W58142, W67781, W67840, W68147, W68474, W68699, W68791, W69717, W80749, W80837, N89879, AA025233, AA025568, AA025686, AA026020, AA033846, AA039625, AA039693, AA046842, AA047013, AA057608, AA057676, AA064637, AA064680, AA074448, AA083591, AA098837, AA102142, AA113374, AA113402, AA115525, AA114948, AA128972, AA128973, AA133142, AA146949, AA148086, AA149283, AA149377, AA160012, AA160688, AA172144, AA180932, AA182561 |
| 783135 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 646 of SEQ ID NO:153, b is an integer of 15 to 660, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:153, and where b is greater than or equal to a + 14. | |
| 783245 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 591 of SEQ ID NO:154, b is an integer of 15 to 605, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:154, and where b is greater than or equal to a + 14. | |
| 783247 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 681 of SEQ ID NO:155, b is an integer of 15 to 695, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:155, and where b is greater than or equal to a + 14. | AA155638 |
| 783413 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide | H58751, H93683, H93684, N93167, W19186, W19958, W38771, N91367 |

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| | sequence described by the general formula of a-b, where a is any integer between 1 to 766 of SEQ ID NO:156, b is an integer of 15 to 780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:156, and where b is greater than or equal to a + 14. | |
| 784407 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1113 of SEQ ID NO:157, b is an integer of 15 to 1127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:157, and where b is greater than or equal to a + 14. | |
| 784548 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1268 of SEQ ID NO:158, b is an integer of 15 to 1282, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:158, and where b is greater than or equal to a + 14. | |
| 785075 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1491 of SEQ ID NO:159, b is an integer of 15 to 1505, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:159, and where b is greater than or equal to a + 14. | |
| 785677 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 722 of SEQ ID NO:160, b is an integer of 15 to 736, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:160, and where b is greater than or equal to a + 14. | |

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| 786238 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 981 of SEQ ID NO:161, b is an integer of 15 to 995, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:161, and where b is greater than or equal to a + 14. | |
| 786389 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:162, b is an integer of 15 to 1125, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:162, and where b is greater than or equal to a + 14. | |
| 786929 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:163, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:163, and where b is greater than or equal to a + 14. | |
| 786932 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1628 of SEQ ID NO:164, b is an integer of 15 to 1642, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:164, and where b is greater than or equal to a + 14. | |
| 787078 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1101 of SEQ ID NO:165, b is an integer of 15 to 1115, where both a and b correspond to the positions of | |

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| | nucleotide residues shown in SEQ ID NO:165, and where b is greater than or equal to a + 14. | |
| 787139 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1052 of SEQ ID NO:166, b is an integer of 15 to 1066, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:166, and where b is greater than or equal to a + 14. | |
| 787283 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:167, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:167, and where b is greater than or equal to a + 14. | R22724 |
| 788761 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1012 of SEQ ID NO:168, b is an integer of 15 to 1026, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:168, and where b is greater than or equal to a + 14. | |
| 788988 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 760 of SEQ ID NO:169, b is an integer of 15 to 774, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:169, and where b is greater than or equal to a + 14. | |
| 789092 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | AA234588 |

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| | between 1 to 388 of SEQ ID NO:170, b is an integer of 15 to 402, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:170, and where b is greater than or equal to a + 14. | |
| 789298 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 782 of SEQ ID NO:171, b is an integer of 15 to 796, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:171, and where b is greater than or equal to a + 14. | |
| 789299 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:172, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:172, and where b is greater than or equal to a + 14. | |
| 789718 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 642 of SEQ ID NO:173, b is an integer of 15 to 656, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:173, and where b is greater than or equal to a + 14. | |
| 789957 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1877 of SEQ ID NO:174, b is an integer of 15 to 1891, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:174, and where b is greater than or equal to a + 14. | T51260, T61941, T62167, T77034, T90753, R38108, N32708, N92379, W24621, W42543, W42478, AA128007, AA128031, AA134234, AA424998 |
| 789977 | Preferably excluded from the present invention are one or more | T56442, T78292, R37940, R56008, R56009, R56573, R56574, H11080, N34431, N48665, |

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| | polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2147 of SEQ ID NO:175, b is an integer of 15 to 2161, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:175, and where b is greater than or equal to a + 14. | AA010749, AA011177, AA070806, AA070882, AA146859, AA147636, AA147691, AA164223, AA164224, AA210729, AA210859, AA243063, AA243070, AA464493, AA464494 |
| 790285 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2397 of SEQ ID NO:176, b is an integer of 15 to 2411, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:176, and where b is greater than or equal to a + 14. | T66279, T66328, T84164, T85098, R24232, R24233, H03657, H03658, H98526, H98556, H99618, N22728, N29400, N32172, N33953, N41460, N69471, N70552, N73722, W03893, W44579, W72407, W76486, W78102, W79410, N90963, AA044816, AA044841, AA086039, AA086121, AA088877, AA102298, AA130887, AA131529, AA131603, AA181784, AA182515, AA190450, AA191392, AA223757 |
| 790509 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1324 of SEQ ID NO:177, b is an integer of 15 to 1338, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:177, and where b is greater than or equal to a + 14. | T68040, H17760, AA101036, AA129837 |
| 790775 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1600 of SEQ ID NO:178, b is an integer of 15 to 1614, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:178, and where b is greater than or equal to a + 14. | N25320, N31432, W81044, W81097 |
| 790888 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4278 of SEQ ID NO:179, b is an integer of 15 to 4292, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:179, and where b is greater than or | R14550, R15204, T26493, R21597, R22908, R23010, R41211, R41649, R43371, R41211, R41649, R43371, R58989, R59048, H05739, H05845, H17266, H17265, H23579, H44104, H46505, H47043, H58955, H59002, H73676, H73730, H80078, H82275, H82289, H82399, H82381, H97810, H98133, H98737, N23117, N24310, N25196, N25265, N27792, N28735, N29893, N33395, N33904, N36066, N36839, N42542, N46060, N51230, N59535, N67737, |

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| | equal to $a + 14$. | N73641, N78481, N78694, W03555, W15202, W52445, W52723, W95124, AA047257, AA057142, AA204699, AA251464, AA430598 |
| 791506 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 229 of SEQ ID NO:180, b is an integer of 15 to 243, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:180, and where b is greater than or equal to $a + 14$. | |
| 791649 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 799 of SEQ ID NO:181, b is an integer of 15 to 813, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:181, and where b is greater than or equal to $a + 14$. | |
| 791802 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 808 of SEQ ID NO:182, b is an integer of 15 to 822, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:182, and where b is greater than or equal to $a + 14$. | |
| 792002 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1081 of SEQ ID NO:183, b is an integer of 15 to 1095, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:183, and where b is greater than or equal to $a + 14$. | T49735, T49736, T95310, T95391, T99384, T99612, R63493, R63494, H27739, R91698, R92136, H52608, H57619, H58464, H61415, H62139, H69019, H87167, H87669, N21358, N70307, N79596, W19063, W58498, W58651, W79687, W81289, AA099849, AA099972, AA232767 |
| 792291 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | T55436, R21797, R22403, R22452, R22916, R23020, R76901, R77068, H22573, H25752, H25866, R83900, H50717, H50821, H64026, H64791, H95702, N64545, N69769, N74704, N80341, W05092, W79489, W79634, |

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| | between 1 to 3661 of SEQ ID NO:184. b is an integer of 15 to 3675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:184, and where b is greater than or equal to a + 14. | AA005055, AA005007, AA025043, AA036711, AA037127, AA043916, AA055100, AA063627, AA069142, AA069230, AA069323, AA069376, AA112277, AA112531, AA115279, AA151238, AA151239, AA151582, AA149398, AA149961, AA150069, AA158029, AA158321, AA158692, AA158693, AA161232, AA236787, AA236834, AA256776, AA261961 |
| 792371 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1026 of SEQ ID NO:185, b is an integer of 15 to 1040, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:185, and where b is greater than or equal to a + 14. | |
| 792660 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 803 of SEQ ID NO:186, b is an integer of 15 to 817, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:186, and where b is greater than or equal to a + 14. | T59054, T86590, T83271, R48677, R53483, R53482, R62329, R62330, R66651, R67372, R69095, R69210, R71144, R82632, R82676, H15764, H15765, H19518, H19605, H27898, H42872, H42936, H49329, H49330, H50062, H50061, H87268, H87324, H96667, N22675, N92574, W37223, W37563, W38866, W61119, W65380, AA035095, AA035635, AA037254, AA054951, AA062973, AA082301, AA132472 |
| 792782 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1066 of SEQ ID NO:187, b is an integer of 15 to 1080, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:187, and where b is greater than or equal to a + 14. | |
| 792890 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1272 of SEQ ID NO:188, b is an integer of 15 to 1286, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:188, and where b is greater than or equal to a + 14. | AA251351 |

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| 792931 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1724 of SEQ ID NO:189, b is an integer of 15 to 1738, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:189, and where b is greater than or equal to a + 14. | |
| 792943 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:190, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:190, and where b is greater than or equal to a + 14. | |
| 793104 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 236 of SEQ ID NO:191, b is an integer of 15 to 250, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:191, and where b is greater than or equal to a + 14. | |
| 793445 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1888 of SEQ ID NO:192, b is an integer of 15 to 1902, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:192, and where b is greater than or equal to a + 14. | AA034998, AA044249, AA088830, AA429418 |
| 793446 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 546 of SEQ ID NO:193, b is an integer of 15 to 560, where both a and b correspond to the positions of | T57765, T60664, H01264, H45774, H54790, H54842, H64484, H64485, N98810, W58332, W58653, W74582, W79320, W79420, W79565, W92452, AA027210, AA027209, AA029725, AA029663, AA088693, AA121506, AA127731, AA428362 |

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| | nucleotide residues shown in SEQ ID NO:193, and where b is greater than or equal to a + 14. | |
| 793639 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 576 of SEQ ID NO:194, b is an integer of 15 to 590, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:194, and where b is greater than or equal to a + 14. | N69881, N93023, N98853, W21375, W73944, W77988, AA169530, AA169837, AA176453, AA176931 |
| 794213 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 677 of SEQ ID NO:195, b is an integer of 15 to 691, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:195, and where b is greater than or equal to a + 14. | N53897, N55318 |
| 795858 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1758 of SEQ ID NO:196, b is an integer of 15 to 1772, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:196, and where b is greater than or equal to a + 14. | |
| 795955 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 661 of SEQ ID NO:197, b is an integer of 15 to 675, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:197, and where b is greater than or equal to a + 14. | |
| 796359 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | |

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| | between 1 to 543 of SEQ ID NO:198, b is an integer of 15 to 557, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:198, and where b is greater than or equal to a + 14. | |
| 796555 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2597 of SEQ ID NO:199, b is an integer of 15 to 2611, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:199, and where b is greater than or equal to a + 14. | T69136, T69194, T95612, T95713, R53091, R73126, N41876, N49174, W05348, W04725, W31397, W31827, W92674, AA039513 |
| 796675 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2302 of SEQ ID NO:200, b is an integer of 15 to 2316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:200, and where b is greater than or equal to a + 14. | |
| 796743 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1133 of SEQ ID NO:201, b is an integer of 15 to 1147, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:201, and where b is greater than or equal to a + 14. | |
| 796792 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 674 of SEQ ID NO:202, b is an integer of 15 to 688, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:202, and where b is greater than or equal to a + 14. | |
| 799668 | Preferably excluded from the present invention are one or more | |

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| | polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 290 of SEQ ID NO:203, b is an integer of 15 to 304, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:203, and where b is greater than or equal to a + 14. | |
| 799669 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 403 of SEQ ID NO:204, b is an integer of 15 to 417, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:204, and where b is greater than or equal to a + 14. | |
| 799673 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 537 of SEQ ID NO:205, b is an integer of 15 to 551, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:205, and where b is greater than or equal to a + 14. | |
| 799674 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1087 of SEQ ID NO:206, b is an integer of 15 to 1101, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:206, and where b is greater than or equal to a + 14. | |
| 799678 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 501 of SEQ ID NO:207, b is an integer of 15 to 515, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:207, and where b is greater than or | |

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| | equal to $a + 14$. | |
| 799728 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 255 of SEQ ID NO:208, b is an integer of 15 to 269, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:208, and where b is greater than or equal to $a + 14$. | |
| 799748 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 720 of SEQ ID NO:209, b is an integer of 15 to 734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:209, and where b is greater than or equal to $a + 14$. | H19497, H19579, H50117, H50164, H52826, H52827, H61184, H62087, H96290, H96291, N20586, N21261, N28978, N30137, N30490, N35750, W31933, W37535, N90542, AA418545, AA418511 |
| 799760 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 644 of SEQ ID NO:210, b is an integer of 15 to 658, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:210, and where b is greater than or equal to $a + 14$. | |
| 799805 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 190 of SEQ ID NO:211, b is an integer of 15 to 204, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:211, and where b is greater than or equal to $a + 14$. | |
| 800296 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1257 of SEQ ID NO:212, b is an integer of 15 to 1271, where both | |

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| | a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:212, and where b is greater than or equal to a + 14. | |
| 800327 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1011 of SEQ ID NO:213, b is an integer of 15 to 1025, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:213, and where b is greater than or equal to a + 14. | |
| 800816 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 337 of SEQ ID NO:214, b is an integer of 15 to 351, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:214, and where b is greater than or equal to a + 14. | |
| 800835 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1073 of SEQ ID NO:215, b is an integer of 15 to 1087, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:215, and where b is greater than or equal to a + 14. | |
| 805429 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1963 of SEQ ID NO:216, b is an integer of 15 to 1977, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:216, and where b is greater than or equal to a + 14. | |
| 805458 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general | T82438, T82439, R19121, R20391, R28602, R36743, R43508, R46035, R43508, R46035, R79588, H24625, N28372, N28785, N29421, N35476, N57353, N72836, N79096, W03034, |

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| | formula of a-b, where a is any integer between 1 to 2801 of SEQ ID NO:217, b is an integer of 15 to 2815, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:217, and where b is greater than or equal to a + 14. | AA016073, AA019733, AA021030, AA062895, AA081968, AA115692, AA133511, AA151852, AA149707, AA194903, AA194902 |
| 805478 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1631 of SEQ ID NO:218, b is an integer of 15 to 1645, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:218, and where b is greater than or equal to a + 14. | |
| 805805 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 464 of SEQ ID NO:219, b is an integer of 15 to 478, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:219, and where b is greater than or equal to a + 14. | |
| 806486 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 818 of SEQ ID NO:220, b is an integer of 15 to 832, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:220, and where b is greater than or equal to a + 14. | |
| 806498 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1878 of SEQ ID NO:221, b is an integer of 15 to 1892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:221, and where b is greater than or equal to a + 14. | |
| 806819 | Preferably excluded from the present | |

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| | invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 854 of SEQ ID NO:222, b is an integer of 15 to 868, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:222, and where b is greater than or equal to a + 14. | |
| 810870 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1502 of SEQ ID NO:223, b is an integer of 15 to 1516, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:223, and where b is greater than or equal to a + 14. | R50267, R50730, H27672, H27673, H30138, H99256, N74342, N80868, W05054, W07601 |
| 811730 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1292 of SEQ ID NO:224, b is an integer of 15 to 1306, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:224, and where b is greater than or equal to a + 14. | |
| 813025 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 570 of SEQ ID NO:225, b is an integer of 15 to 584, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:225, and where b is greater than or equal to a + 14. | |
| 813233 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 509 of SEQ ID NO:226, b is an integer of 15 to 523, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID | |

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| | NO:226, and where b is greater than or equal to $a + 14$. | |
| 813262 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2363 of SEQ ID NO:227, b is an integer of 15 to 2377, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:227, and where b is greater than or equal to $a + 14$. | |
| 815637 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 449 of SEQ ID NO:228, b is an integer of 15 to 463, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:228, and where b is greater than or equal to $a + 14$. | |
| 815853 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1218 of SEQ ID NO:229, b is an integer of 15 to 1232, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:229, and where b is greater than or equal to $a + 14$. | R53293, R59708, R59818, R88929, R89609, H78819, N52182, AA125808, AA128281 |
| 815999 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:230, b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:230, and where b is greater than or equal to $a + 14$. | |
| 823427 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1049 of SEQ ID NO:231, | T53986, T60846, T72425, R18752, H22479, H50211, N40817, N93431, W21474, W21308, W32281, W44860, W95821, N90881, AA132037, AA131965, AA151157, AA155868, AA156600, AA156837, AA157061, AA157045, AA160623, AA169460, AA176447, AA178894, |

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| | b is an integer of 15 to 1063, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:231, and where b is greater than or equal to a + 14. | AA179764, AA180438, AA181145, AA181144, AA196382, AA196478 |
| 823704 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1460 of SEQ ID NO:232, b is an integer of 15 to 1474, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:232, and where b is greater than or equal to a + 14. | |
| 824798 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1768 of SEQ ID NO:233, b is an integer of 15 to 1782, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:233, and where b is greater than or equal to a + 14. | |
| 825018 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2194 of SEQ ID NO:234, b is an integer of 15 to 2208, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:234, and where b is greater than or equal to a + 14. | |
| 825076 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2566 of SEQ ID NO:235, b is an integer of 15 to 2580, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:235, and where b is greater than or equal to a + 14. | |
| 825787 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide | |

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| | sequence described by the general formula of a-b, where a is any integer between 1 to 2994 of SEQ ID NO:236, b is an integer of 15 to 3008, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:236, and where b is greater than or equal to a + 14. | |
| 826116 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 863 of SEQ ID NO:237, b is an integer of 15 to 877, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:237, and where b is greater than or equal to a + 14. | |
| 826147 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3025 of SEQ ID NO:238, b is an integer of 15 to 3039, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:238, and where b is greater than or equal to a + 14. | |
| 827020 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1978 of SEQ ID NO:239, b is an integer of 15 to 1992, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:239, and where b is greater than or equal to a + 14. | |
| 827586 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 483 of SEQ ID NO:240, b is an integer of 15 to 497, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:240, and where b is greater than or equal to a + 14. | |

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| 827732 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 302 of SEQ ID NO:241, b is an integer of 15 to 316, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:241, and where b is greater than or equal to a + 14. | |
| 827735 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 815 of SEQ ID NO:242, b is an integer of 15 to 829, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:242, and where b is greater than or equal to a + 14. | |
| 827740 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 824 of SEQ ID NO:243, b is an integer of 15 to 838, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:243, and where b is greater than or equal to a + 14. | R21513, R22316, R42033, R43706, R42033, R43706, R63113, R70954, R71006, N48618, N53377, AA912400 |
| 827808 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2839 of SEQ ID NO:244, b is an integer of 15 to 2853, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:244, and where b is greater than or equal to a + 14. | |
| 828251 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1183 of SEQ ID NO:245, b is an integer of 15 to 1197, where both a and b correspond to the positions of | |

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| | nucleotide residues shown in SEQ ID NO:245, and where b is greater than or equal to a + 14. | |
| 828357 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 834 of SEQ ID NO:246, b is an integer of 15 to 848, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:246, and where b is greater than or equal to a + 14. | |
| 828449 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1322 of SEQ ID NO:247, b is an integer of 15 to 1336, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:247, and where b is greater than or equal to a + 14. | |
| 828612 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1062 of SEQ ID NO:248, b is an integer of 15 to 1076, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:248, and where b is greater than or equal to a + 14. | R28513, R28661, R31336, R41867, R41867, R60004, H19945, H19946, H22061, H46271, H46342, H82619, H82618, N20678, W96169, AA010842, AA278855, AA582295, AA583721, AA639735, AA579409, AA568321, AA833752, AA907437, AI054389, W22584 |
| 828647 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2411 of SEQ ID NO:249, b is an integer of 15 to 2425, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:249, and where b is greater than or equal to a + 14. | |
| 828698 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | |

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| | between 1 to 1394 of SEQ ID NO:250, b is an integer of 15 to 1408, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:250, and where b is greater than or equal to a + 14. | |
| 828962 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 480 of SEQ ID NO:251, b is an integer of 15 to 494, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:251, and where b is greater than or equal to a + 14. | |
| 828982 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2477 of SEQ ID NO:252, b is an integer of 15 to 2491, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:252, and where b is greater than or equal to a + 14. | T64550, T65973, T94849, T94894, R07359, R07409, R34782, R35670, R35781, R56137, R56532, R64039, R66397, R67131, H01215, H02256, H02354, H03227, H04019, R94572, R94573, H51242, H60286, H65939, H72416, H72857, N22537, N24628, N24936, N33813, N35712, N35830, N35916, N43982, N51363, N64462, N70838, N75470, N75760, W01444, W05279, W57605, W58752, W72612, W72970, W73260, W73535, W76678, W76207, W94918, W91971, W92319, W92355, AA024690, AA024643, AA028083, AA028084, AA028169, AA035743, AA045830, AA045917, AA081723, AA086310, AA085740, AA102651, AA101305, AA126788, AA126837, AA126865, AA127295, AA129688, AA129664, AA133503, AA133504, AA132801, AA134537, AA134547, AA186712, AA188264, AA215597, AA463977, AA464112, AA417286, AA417312, AA259228, AA279952, AA287814, AA468227, AA468302, AA526480, AA553703, AA587072, AA635683, AA639361, AA573471, AA579754, AA579812, AA580600, AA730425, AA741436, AA804629, AA829189, AA830255, AA865594, AA885821, AA918979, AA962033, AA985542, AA985571, AA987607, AA995783, AI075334, D79160, N84712, N88655, C03235, AA094028 |
| 829282 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1111 of SEQ ID NO:253, b is an integer of 15 to 1125, where both a and b correspond to the positions of | |

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| | nucleotide residues shown in SEQ ID NO:253, and where b is greater than or equal to a + 14. | |
| 829368 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1395 of SEQ ID NO:254, b is an integer of 15 to 1409, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:254, and where b is greater than or equal to a + 14. | R61547, R76124, H01565, H02950, H04248, H29996, H99672, W19970 |
| 829751 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 476 of SEQ ID NO:255, b is an integer of 15 to 490, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:255, and where b is greater than or equal to a + 14. | |
| 829773 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1219 of SEQ ID NO:256, b is an integer of 15 to 1233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:256, and where b is greater than or equal to a + 14. | T96982, T97094, H53488, H53861, H64894, H65486, N62304, N67480, N78709, W03409, W07598, W73770, AA025496, AA025812, AA133948 |
| 829934 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2390 of SEQ ID NO:257, b is an integer of 15 to 2404, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:257, and where b is greater than or equal to a + 14. | |
| 829942 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | T64541, T65964, R01423, R01424, R05277, R19450, R44699, R51779, R51780, R44699, H11322, H11349, H13859, H13911, H21393, H21437, H21890, H22117, H45982, H46047, H47137, R98886, H54491, H54854, H98744, |

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| | between 1 to 2078 of SEQ ID NO:258, b is an integer of 15 to 2092, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:258, and where b is greater than or equal to a + 14. | N23465, N37080, N46155, N46396, N58995, N62715, N93640, W60228, W60227, W74349, W76544, W87768, W87883, W90517, W90518, AA010775, AA011055, AA029083, AA029084, AA036822, AA057660, AA075916, AA082814, AA101057, AA130702, AA132788, AA133063, AA147813, AA148063, AA151487, AA151511, AA173298, AA173348, AA181036, AA187993, AA187994, AA192370, AA192357, AA243010, AA243264, AA250948 |
| 829951 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 373 of SEQ ID NO:259, b is an integer of 15 to 387, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:259, and where b is greater than or equal to a + 14. | |
| 830173 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3698 of SEQ ID NO:260, b is an integer of 15 to 3712, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:260, and where b is greater than or equal to a + 14. | T52493, T52572, T56913, T61268, T61320, T70063, T70130, T72005, T87844, T94182, T70248, R24534, R24639, R31200, R64161, R64274, R70751, R70750, H16189, H89274, H99749, N25430, N25537, N32578, N32816, N34120, N34134, N34491, N35081, N42260, N43821, N62152, N62798, N64065, N64169, N67362, N69808, N74678, N93912, N49165, W04704, W05040, W16565, W19920, W31806, W31907, W37354, W37355, W40493, W45266, W45455, W52925, W58628, W92222, W92345, N91265, AA027083, AA027124, AA028969, AA029137, AA029257, AA083657, AA084297, AA121151, AA121131, AA126957, AA127166, AA128353, AA128495, AA128834, AA132690, AA132783, AA136553, AA152414, AA150706, AA150808, AA156272, AA164766, AA164767, AA171427, AA171794, AA173592, AA173949, AA190421, AA190580, AA191383, AA224415, AA232135 |
| 830200 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 883 of SEQ ID NO:261, b is an integer of 15 to 897, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:261, and where b is greater than or equal to a + 14. | AA524284, AA662477, AA887924 |

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| 830365 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1891 of SEQ ID NO:262, b is an integer of 15 to 1905, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:262, and where b is greater than or equal to a + 14. | R42905, R59718, R62419, R72182, R72228, H22520, H22519, H25889, H45643, H46451, H46992, H84483, N50834, N92573, AA022699, AA022791, AA037734, AA037735, AA040585, AA040557, AA047816, AA159187, AA159282, AA223337, AA505391, AA515591, AA524466, AA613383, AA627298, AA578816, AA769153, AA826456, AA830896, AA831083, AA837917, AA977053, AI083822, AI090301, AI084104 |
| 830456 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1410 of SEQ ID NO:263, b is an integer of 15 to 1424, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:263, and where b is greater than or equal to a + 14. | T39800, T39875, T40331, T80148, R01135, R05754, R12866, R15287, R21703, R39361, H00652, H00741, H05366, H17706, H23423, R97800, R97849, N25478, N41797, N48511, N98906, W19893, W23945, W35174, W60540, W78229, W79282, W84685, AA022952, AA026821, AA026953, AA074956, AA075111, AA114974, AA114988, AA192860, AA193064 |
| 830549 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1273 of SEQ ID NO:264, b is an integer of 15 to 1287, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:264, and where b is greater than or equal to a + 14. | R60171, H26796, H96303, N91699, W25137, AA069218, AA088565, AA161178 |
| 830602 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 977 of SEQ ID NO:265, b is an integer of 15 to 991, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:265, and where b is greater than or equal to a + 14. | |
| 830610 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2306 of SEQ ID NO:266, b is an integer of 15 to 2320, where both a and b correspond to the positions of | |

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| | nucleotide residues shown in SEQ ID NO:266, and where b is greater than or equal to a + 14. | |
| 830644 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 409 of SEQ ID NO:267, b is an integer of 15 to 423, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:267, and where b is greater than or equal to a + 14. | |
| 830707 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1832 of SEQ ID NO:268, b is an integer of 15 to 1846, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:268, and where b is greater than or equal to a + 14. | |
| 830709 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 587 of SEQ ID NO:269, b is an integer of 15 to 601, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:269, and where b is greater than or equal to a + 14. | |
| 830733 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 866 of SEQ ID NO:270, b is an integer of 15 to 880, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:270, and where b is greater than or equal to a + 14. | T26638, R49962, H96664, N71762, N90691, AA040156, AA128271, AA418045, AA418216, AA535799, AA583405, AA768811 |
| 830768 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | |

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| | between 1 to 2470 of SEQ ID NO:271, b is an integer of 15 to 2484, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:271, and where b is greater than or equal to a + 14. | |
| 830855 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 737 of SEQ ID NO:272, b is an integer of 15 to 751, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:272, and where b is greater than or equal to a + 14. | H17127, AA100311, AA112910, AA282249, AA578649, AA748590 |
| 830949 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3295 of SEQ ID NO:273, b is an integer of 15 to 3309, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:273, and where b is greater than or equal to a + 14. | |
| 830965 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 829 of SEQ ID NO:274, b is an integer of 15 to 843, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:274, and where b is greater than or equal to a + 14. | |
| 830973 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2014 of SEQ ID NO:275, b is an integer of 15 to 2028, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:275, and where b is greater than or equal to a + 14. | |
| 830979 | Preferably excluded from the present invention are one or more | |

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| | polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1441 of SEQ ID NO:276, b is an integer of 15 to 1455, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:276, and where b is greater than or equal to a + 14. | |
| 830989 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1909 of SEQ ID NO:277, b is an integer of 15 to 1923, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:277, and where b is greater than or equal to a + 14. | |
| 831134 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1366 of SEQ ID NO:278, b is an integer of 15 to 1380, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:278, and where b is greater than or equal to a + 14. | |
| 831200 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1004 of SEQ ID NO:279, b is an integer of 15 to 1018, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:279, and where b is greater than or equal to a + 14. | |
| 831260 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1178 of SEQ ID NO:280, b is an integer of 15 to 1192, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:280, and where b is greater than or | R15008, R28066, R68324, H20638, N25438, N67982, N67983, N67999, N68004, N68005, N80403, N80423, N80429, N80430, AA024581, AA024582, AA024637, AA862760, AA091142 |

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| | equal to $a + 14$. | |
| 831531 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1741 of SEQ ID NO:281, b is an integer of 15 to 1755, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:281, and where b is greater than or equal to $a + 14$. | T66624, R16038, R26139, R26353, H15795, H16285, H21749, H21945, H22698, H23978, H52286, H52523, H60184, H60227, H68044, H81748, H81749, N46859, N47179, N51722, N51808, AA031701, AA031866, AA043760, AA043761, AA081005, AA081148, AA195519, AA470636, AA534463, AA555198, AA631348, AA721036, AA737025, AA761301, AA764993, AA765314, AA765749, AA878422, U47720, C21223 |
| 831665 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1079 of SEQ ID NO:282, b is an integer of 15 to 1093, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:282, and where b is greater than or equal to $a + 14$. | |
| 831724 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1542 of SEQ ID NO:283, b is an integer of 15 to 1556, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:283, and where b is greater than or equal to $a + 14$. | R52161, N45179, N68350, N94021, W02782, W24840, W61323, AA907441 |
| 831884 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1015 of SEQ ID NO:284, b is an integer of 15 to 1029, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:284, and where b is greater than or equal to $a + 14$. | |
| 831897 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of $a-b$, where a is any integer between 1 to 1569 of SEQ ID NO:285, b is an integer of 15 to 1583, where both | AA056348, AA127534 |

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| | a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:285, and where b is greater than or equal to a + 14. | |
| 831922 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1163 of SEQ ID NO:286, b is an integer of 15 to 1177, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:286, and where b is greater than or equal to a + 14. | |
| 831963 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 492 of SEQ ID NO:287, b is an integer of 15 to 506, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:287, and where b is greater than or equal to a + 14. | |
| 832074 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 934 of SEQ ID NO:288, b is an integer of 15 to 948, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:288, and where b is greater than or equal to a + 14. | |
| 832266 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1020 of SEQ ID NO:289, b is an integer of 15 to 1034, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:289, and where b is greater than or equal to a + 14. | T70612, T70879, H13555, H23264, R97792, R97842, N75850, W07434, W19866, N90056, AA043395, AA463232, AA463231 |
| 832309 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general | |

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| | formula of a-b, where a is any integer between 1 to 3077 of SEQ ID NO:290, b is an integer of 15 to 3091, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:290, and where b is greater than or equal to a + 14. | |
| 832342 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 504 of SEQ ID NO:291, b is an integer of 15 to 518, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:291, and where b is greater than or equal to a + 14. | |
| 832351 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 484 of SEQ ID NO:292, b is an integer of 15 to 498, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:292, and where b is greater than or equal to a + 14. | |
| 832352 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 455 of SEQ ID NO:293, b is an integer of 15 to 469, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:293, and where b is greater than or equal to a + 14. | |
| 832434 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 654 of SEQ ID NO:294, b is an integer of 15 to 668, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:294, and where b is greater than or equal to a + 14. | |
| 832490 | Preferably excluded from the present | T86496, H24346, R84505, N26874, N98621, |

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| | invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1386 of SEQ ID NO:295, b is an integer of 15 to 1400, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:295, and where b is greater than or equal to a + 14. | W04678, W04692, W24267, W93387, W94971, AA036953, AA136869, AA136799, AA147214, AA160413, AA535592, AA931261, AA931403, AA962726, AA992456 |
| 832573 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 946 of SEQ ID NO:296, b is an integer of 15 to 960, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:296, and where b is greater than or equal to a + 14. | |
| 832580 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 643 of SEQ ID NO:297, b is an integer of 15 to 657, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:297, and where b is greater than or equal to a + 14. | |
| 833394 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 878 of SEQ ID NO:298, b is an integer of 15 to 892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:298, and where b is greater than or equal to a + 14. | |
| 835355 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:299, b is an integer of 15 to 1624, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID | AA076638, AA916592, AI088936, AI089690 |

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| | NO:299, and where b is greater than or equal to a + 14. | |
| 835497 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1955 of SEQ ID NO:300, b is an integer of 15 to 1969, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:300, and where b is greater than or equal to a + 14. | |
| 835728 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1868 of SEQ ID NO:301, b is an integer of 15 to 1882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:301, and where b is greater than or equal to a + 14. | |
| 835978 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2790 of SEQ ID NO:302, b is an integer of 15 to 2804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:302, and where b is greater than or equal to a + 14. | |
| 836091 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3845 of SEQ ID NO:303, b is an integer of 15 to 3859, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:303, and where b is greater than or equal to a + 14. | R02093, R02205, R02336, R02439, R19436, R44685, R44685, R72354, H10160, H49884, H49885, N23208, N28789, N29901, N42953, N55093, N77305, N99373, W46396, W46504, AA082311, AA176281, AA176282, AA227971, AA228079, AA234964, AA234145, AA281787, AA281656, AA524468, AA551888, AA631173, AA639499, AA811344, AA830439, AA831974, AA923665, C03439, AA641655, AA091346, AA400968, AA400884 |
| 836274 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 3364 of SEQ ID NO:304, | T75442, R20393, R43511, R43511, R73650, R73731, R80152, R80886, H97932, H98616, N33018, N71679, N99650, AA001053, AA001089, AA044947, AA044943, AA149057, AA464856, AA427892, AA228265, AA230021, AA482694, AA483691, AA484850, AA513037, |

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| | b is an integer of 15 to 3378, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:304, and where b is greater than or equal to a + 14. | AA516076, AA532381, AA583355, AA618566, AA577028, AA730651, AA730790, AA745667, AA829807, AA923038, AA931937, AA932867, AA934400, AA934413, AA971551, AA971743, AA972772, AA977253, AA992454, AA994794, A1089906, A1094921, D79281, C06099, D44840, C20741, AA283186, AA292346, AA394164 |
| 836731 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1000 of SEQ ID NO:305, b is an integer of 15 to 1014, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:305, and where b is greater than or equal to a + 14. | |
| 838014 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2113 of SEQ ID NO:306, b is an integer of 15 to 2127, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:306, and where b is greater than or equal to a + 14. | |
| 838874 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 652 of SEQ ID NO:307, b is an integer of 15 to 666, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:307, and where b is greater than or equal to a + 14. | R61165, N44200 |
| 839120 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2157 of SEQ ID NO:308, b is an integer of 15 to 2171, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:308, and where b is greater than or equal to a + 14. | T74462, R18264, H23432, AA279685, AA847441, AA904076, AA393782 |

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| 839611 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 6149 of SEQ ID NO:309, b is an integer of 15 to 6163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:309, and where b is greater than or equal to a + 14. | T93695, T93696, T96161, R32227, R32254, R32304, R33503, R34044, R71178, H93366, N50709, N55039, AA165143, AA199856, AA199927, AA234331, AA262892, AA423987, AA423986, AA525886, AA661602, AA731504, AA741228, AA814795, AA828858, AA829196, AA831198, AA834822, AA865590, AA886436, AA903649, D82270, D82453, D82464, AA642466, AA219620, AA219628, AA400707, AA400674, AA421941, AA633988, AA663219, AA663250, AA665538, AA724260, AI074714, T26891, T26926 |
| 840138 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2072 of SEQ ID NO:310, b is an integer of 15 to 2086, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:310, and where b is greater than or equal to a + 14. | |
| 840616 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2149 of SEQ ID NO:311, b is an integer of 15 to 2163, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:311, and where b is greater than or equal to a + 14. | |
| 840780 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1383 of SEQ ID NO:312, b is an integer of 15 to 1397, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:312, and where b is greater than or equal to a + 14. | |
| 840857 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 4092 of SEQ ID NO:313, b is an integer of 15 to 4106, where both | T50389, T50520, T55419, T55495, T55974, T57220, R34591, R34592, R69726, H21148, R85777, R99233, H61311, H62351, H85185, H88299, N23288, N32662, N58504, N78093, N92665, N99611, AA005068, AA007333, AA007334, AA036884, AA044715, AA045458, AA046500, AA045654, AA115936, AA121004, |

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| | a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:313, and where b is greater than or equal to a + 14. | AA126775, AA133605, AA133606, AA133980, AA181633, AA182611, AA232979, AA233365, AA459953, AA460042, AA282826, AA285050, AA506082, AA558006, AA601060, AA767799, AA804323, AA807029, AA807087, AA825536, AA833810, AA922732, AA928638, AA960990, N56482, N62047, W27456, W26569, AA092778, AA652535, AA065256, AA065257, AA450197, AA452846, AA452986, AA705224, Z19460, AA884767, AA969488, AA977494, AI002996, AI032008, Z28526, D20112, T19336 |
| 840862 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 518 of SEQ ID NO:314, b is an integer of 15 to 532, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:314, and where b is greater than or equal to a + 14. | T94528, N40545, N46592, N92934, AA570273, AA873604, AA910827, AA932397, AA971868, AI095210, N56229, AA648290, F20835, AA629912 |
| 840864 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1924 of SEQ ID NO:315, b is an integer of 15 to 1938, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:315, and where b is greater than or equal to a + 14. | R40870, R44820, H26640, W78814, W80713, AA195492, AA937549, AI085492, AI094865, AA449317, AA884600, AA909529, AA923452, AA971781, AI084795, AI089007, AA702758, AA702769 |
| 840936 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 804 of SEQ ID NO:316, b is an integer of 15 to 818, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:316, and where b is greater than or equal to a + 14. | |
| 840938 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 823 of SEQ ID NO:317, b is an integer of 15 to 837, where both a and b correspond to the positions of | |

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| | nucleotide residues shown in SEQ ID NO:317, and where b is greater than or equal to a + 14. | |
| 841884 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1434 of SEQ ID NO:318, b is an integer of 15 to 1448, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:318, and where b is greater than or equal to a + 14. | |
| 842241 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1479 of SEQ ID NO:319, b is an integer of 15 to 1493, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:319, and where b is greater than or equal to a + 14. | |
| 843712 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 595 of SEQ ID NO:320, b is an integer of 15 to 609, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:320, and where b is greater than or equal to a + 14. | R02291, N94598, W85882, AA255975 |
| 844040 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 488 of SEQ ID NO:321, b is an integer of 15 to 502, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:321, and where b is greater than or equal to a + 14. | W24428, AA143434, AA459809 |
| 844336 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer | |

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| | between 1 to 2616 of SEQ ID NO:322, b is an integer of 15 to 2630, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:322, and where b is greater than or equal to a + 14. | |
| 844612 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1860 of SEQ ID NO:323, b is an integer of 15 to 1874, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:323, and where b is greater than or equal to a + 14. | |
| 844617 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2311 of SEQ ID NO:324, b is an integer of 15 to 2325, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:324, and where b is greater than or equal to a + 14. | |
| 845251 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:325, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:325, and where b is greater than or equal to a + 14. | T68474, AA159183, AA464447, AA424290, AA424487, AA631793, AA928390, AA946921, AA975194, AA977141, AA430527, AA430612, AA477798 |
| 845764 | Preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 230 of SEQ ID NO:326, b is an integer of 15 to 244, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:326, and where b is greater than or equal to a + 14. | |
| 846187 | Preferably excluded from the present invention are one or more | |

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| | polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2440 of SEQ ID NO:327, b is an integer of 15 to 2454, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:327, and where b is greater than or equal to a + 14. | |
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Polynucleotide and Polypeptide Variants

The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X or the complementary strand thereto, and/or the cDNA sequence contained in a cDNA clone contained in the deposit.

5 The present invention also encompasses variants of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide sequence disclosed in SEQ ID NO:Y, a polypeptide sequence encoded by the polynucleotide sequence in SEQ ID NO:X, and/or a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

10 "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 15 97%, 98%, 99% or 100%, identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence of the related cDNA contained in a deposited library or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide 20 sequence encoding the polypeptide encoded by the cDNA in the related cDNA contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polypeptides encoded by these nucleic acid molecules are also encompassed by the invention. In another embodiment, the invention encompasses nucleic acid molecules which comprise or alternatively consist of, a 25 polynucleotide which hybridizes under stringent hybridization conditions, or alternatively, under low stringency conditions, to the nucleotide coding sequence in SEQ ID NO:X, the

nucleotide coding sequence of the related cDNA clone contained in a deposited library, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a nucleotide sequence encoding the polypeptide encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, a polypeptide sequence encoded by the nucleotide sequence in SEQ ID NO:X, a polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein). Polynucleotides which hybridize to the complement of the nucleic acid molecules encoding these polypeptides under stringent hybridization conditions, or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be, for example, an entire sequence referred to in Table I, an ORF (open reading frame), or any fragment specified as described herein.

As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of

the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the
5 algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245 (1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to
10 calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results.
15 This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a
20 nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment,
25 which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at
30 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases

were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, the amino acid sequence in SEQ ID NO:Y or a fragment thereof, the amino acid sequence encoded by the nucleotide sequence in SEQ ID NO:X or a fragment thereof, or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library, or a fragment thereof, can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci.6:237- 245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window

Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results.

5 This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject
10 residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues
15 to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C- terminal residues of the subject sequence.

For example, a 90 amino acid residue subject sequence is aligned with a 100 residue
20 query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C- termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the
25 FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected.
30 Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to made for the

purposes of the present invention.

The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which less than 50, less than 40, less than 30, less than 20, less than 10, or 5-50, 5-25, 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the polypeptides of the present invention. For instance, as discussed herein, one or more amino acids can be deleted from the N-terminus or C-terminus of the polypeptide of the present invention without substantial loss of biological function. The authors of Ron et al., *J. Biol. Chem.* 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., *J. Biotechnology* 7:199-216 (1988).)

Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (*J. Biol. Chem.* 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that

"[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

5 Furthermore, as discussed herein, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are
10 removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

Thus, the invention further includes polypeptide variants which show a functional activity (e.g., biological activity) of the polypeptide of the invention of which they are a
15 variant. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the art so as have little effect on activity.

The present application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed herein or fragments thereof, (e.g., including but not limited to fragments encoding a polypeptide
20 having the amino acid sequence of an N and/or C terminal deletion), irrespective of whether they encode a polypeptide having functional activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having functional activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid
25 molecules of the present invention that do not encode a polypeptide having functional activity include, inter alia, (1) isolating a gene or allelic or splice variants thereof in a cDNA library; (2) in situ hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the gene, as described in Verma et al., Human Chromosomes: A Manual of Basic Techniques, Pergamon Press, New York (1988); and (3) Northern Blot
30 analysis for detecting mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% or 100% identical to the nucleic acid sequences disclosed

herein, which do, in fact, encode a polypeptide having a functional activity of a polypeptide of the invention.

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to, for example, the nucleic acid sequence of the cDNA in the related cDNA clone contained in a deposited library, the nucleic acid sequence referred to in Table 1 (SEQ ID NO:X), or fragments thereof, will encode polypeptides "having functional activity." In fact, since degenerate variants of any of these nucleotide sequences all encode the same polypeptide, in many instances, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having functional activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid), as further described below.

For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells,

Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly. Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues, where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30

amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course it is highly preferable for a polypeptide to have an amino acid sequence which comprises the amino acid sequence of a polypeptide of SEQ ID NO:Y, an amino acid sequence encoded by SEQ ID NO:X, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library which contains, in order of ever-increasing preference, at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of SEQ ID NO:Y or fragments thereof (e.g., the mature form and/or other fragments described herein), an amino acid sequence encoded by SEQ ID NO:X or fragments thereof, and/or the amino acid sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or fragments thereof, is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Polynucleotide and Polypeptide Fragments

The present invention is also directed to polynucleotide fragments of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides (nucleic acids) of the invention. In the present invention, a "polynucleotide fragment" refers, for example, to a polynucleotide having a nucleic acid sequence which: is a portion of the cDNA contained in a deposited cDNA clone; or is a portion of a polynucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited cDNA clone; or is a portion of the polynucleotide sequence in SEQ ID NO:X or the complementary strand thereto; or is a polynucleotide sequence encoding a portion of the polypeptide of SEQ ID NO:Y; or is a polynucleotide sequence encoding a portion of a polypeptide encoded by SEQ ID NO:X or the complementary strand thereto. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, at least about 100 nt, at least about 125 nt or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from, for example, the sequence contained in the cDNA in a related cDNA clone contained in a deposited library, the nucleotide sequence shown in SEQ ID NO:X or the complementary strand thereto. In this context "about" includes the particularly recited value or a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides. These nucleotide fragments have uses that

include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., at least 150, 175, 200, 250, 500, 600, 1000, or 2000 nucleotides in length) are also encompassed by the invention.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of SEQ ID NO:X, or the complementary strand thereto. In this context "about" includes the particularly recited range or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the polynucleotide of which the sequence is a portion. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these nucleic acid molecules under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from

about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, 2001-2050, 2051-2100, 2101-2150, 2151-2200, 2201-2250, 2251-2300, 2301-2350, 2351-2400, 2401-2450, 2451-2500, 2501-2550, 2551-2600, 2601-2650, 2651-2700, 2701-2750, 2751-2800, 2801-2850, 2851-2900, 2901-2950, 2951-3000, 3001-3050, 3051-3100, 3101-3150, 3151-3200, 3201-3250, 3251-3300, 3301-3350, 3351-3400, 3401-3450, 3451-3500, 3501-3550, 3551-3600, 3601-3650, 3651-3700, 3701-3750, 3751-3800, 3801-3850, 3851-3900, 3901-3950, 3951-4000, 4001-4050, 4051-4100, 4101-4150, 4151-4200, 4201-4250, 4251-4300, 4301-4350, 4351-4400, 4401-4450, 4451-4500, 4501-4550, 4551-4600, 4601-4650, 4651-4700, 4701-4750, 4751-4800, 4801-4850, 4851-4900, 4901-4950, 4951-5000, 5001-5050, 5051-5100, 5101-5150, 5151-5200, 5201-5250, 5251-5300, 5301-5350, 5351-5400, 5401-5450, 5451-5500, 5501-5550, 5551-5600, 5601-5650, 5651-5700, 5701-5750, 5751-5800, 5801-5850, 5851-5900, 5901-5950, 5951-6000, 6001-6050, 6051-6100, 6101-6150, and 6151 to the end of the cDNA nucleotide sequence contained in the deposited cDNA clone, or the complementary strand thereto. In this context "about" includes the particularly recited range, or a range larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has a functional activity (e.g., biological activity) of the polypeptide encoded by the cDNA nucleotide sequence contained in the deposited cDNA clone. More preferably, these fragments can be used as probes or primers as discussed herein. Polynucleotides which hybridize to one or more of these fragments under stringent hybridization conditions or alternatively, under lower stringency conditions, are also encompassed by the invention, as are polypeptides encoded by these polynucleotides or fragments.

In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y, a portion of an amino acid sequence encoded by the polynucleotide sequence of SEQ ID NO:X, and/or encoded by the cDNA contained in the related cDNA clone contained in a deposited library. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region.

Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, an amino acid sequence from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, 281-300, 301-320, 321-340, 341-360, 361-380, 381-400, 401-420, 421-440, 441-460, 461-480, 481-500, 501-520, 521-540, 541-560, 561-580, 581-600, 601-620, 621-640, 641-660, 661-680, 681-700, 701-720, 721-740, 741-760, 761-780, 781-800, 801-820, 821-840, 841-860, 861-880, 881-900, 901-920, 921-940, 941-960, 961-980, 981-1000, 1001-1020, 1021-1040, 1041-1060, 1061-1080, 1081-1100, 1101-1120, 1121-1140, 1141-1160, 1161-1180, 1181-1200, 1201-1220, 1221-1240, 1241-1260, 1261-1280, 1281-1300, 1301-1320, 1321-1340, 1341-1360, 1361-1380, 1381-1400, 1401-1420, 1421-1440, 1441-1460, 1461-1480, 1481-1500, 1501-1520, 1521-1540, 1541-1560, 1561-1580, 1581-1600, 1601-1620, 1621-1640, 1641-1660, 1661-1680, 1681-1700, 1701-1720, 1721-1740, 1741-1760, 1761-1780, 1781-1800, 1801-1820, 1821-1840, 1841-1860, 1861-1880, 1881-1900, 1901-1920, 1921-1940, 1941-1960, 1961-1980, and 1981 to the end of SEQ ID NO:Y. Moreover, polypeptide fragments of the invention may be at least about 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, or ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either terminus or at both termini. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

Even if deletion of one or more amino acids from the N-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example, the ability of shortened muteins to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptides generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the N-terminus. Whether a particular polypeptide lacking N-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted N-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, polypeptide fragments of the invention include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form. Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

The present invention further provides polypeptides having one or more residues deleted from the amino terminus of the amino acid sequence of a polypeptide disclosed herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in the related cDNA clone contained in a deposited library). In particular, N-terminal deletions may be described by the general formula m-q, where q is a whole integer representing the total number of amino acid residues in a polypeptide of the invention (e.g., the polypeptide disclosed in SEQ ID NO:Y), and m is defined as any integer ranging from 2 to q-6. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind a ligand) may still be retained. For example the ability of the shortened mutein to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a mutein with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

Accordingly, the present invention further provides polypeptides having one or more residues from the carboxy terminus of the amino acid sequence of a polypeptide disclosed

herein (e.g., a polypeptide of SEQ ID NO:Y, a polypeptide encoded by the polynucleotide sequence contained in SEQ ID NO:X, and/or a polypeptide encoded by the cDNA contained in deposited cDNA clone referenced in Table I). In particular, C-terminal deletions may be described by the general formula 1-n, where n is any whole integer ranging from 6 to q-1, and where n corresponds to the position of an amino acid residue in a polypeptide of the invention. Polynucleotides encoding these polypeptides are also encompassed by the invention.

In addition, any of the above described N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides having one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of a polypeptide encoded by SEQ ID NO:X (e.g., including, but not limited to, the preferred polypeptide disclosed as SEQ ID NO:Y), and/or the cDNA in the related cDNA clone contained in a deposited library, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Any polypeptide sequence contained in the polypeptide of SEQ ID NO:Y, encoded by the polynucleotide sequences set forth as SEQ ID NO:X, or encoded by the cDNA in the related cDNA clone contained in a deposited library may be analyzed to determine certain preferred regions of the polypeptide. For example, the amino acid sequence of a polypeptide encoded by a polynucleotide sequence of SEQ ID NO:X, or the cDNA in a deposited cDNA clone may be analyzed using the default parameters of the DNASTAR computer algorithm (DNASTAR, Inc., 1228 S. Park St., Madison, WI 53715 USA; <http://www.dnastar.com/>).

Polypeptide regions that may be routinely obtained using the DNASTAR computer algorithm include, but are not limited to, Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and turn-regions, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. Among highly preferred polynucleotides of the invention in this regard are those that encode polypeptides comprising regions that combine several structural features, such as several (e.g., 1, 2, 3 or 4) of the features set out above.

Additionally, Kyte-Doolittle hydrophilic regions and hydrophobic regions, Emini surface-forming regions, and Jameson-Wolf regions of high antigenic index (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) can routinely be used to determine polypeptide regions that exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from data by DNASTAR analysis by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Preferred polypeptide fragments of the invention are fragments comprising, or alternatively consisting of, an amino acid sequence that displays a functional activity of the polypeptide sequence of which the amino acid sequence is a fragment.

By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) protein of the invention. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide for binding) to an anti-polypeptide antibody], immunogenicity (ability to generate antibody which binds to a specific polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide.

Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

In preferred embodiments, polypeptides of the invention comprise, or alternatively consist of, one, two, three, four, five or more of the antigenic fragments of the polypeptide of SEQ ID NO:Y, or portions thereof. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Table 4

| Sequence/ Contig ID | Epitope |
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| 508678 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 422 as residues: Gln-21 to Arg-43. |
| 508968 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 423 as residues: Thr-1 to Lys-6. |
| 509029 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 424 as residues: Asp-1 to Trp-8, Thr-12 to Cys-19, Pro-41 to Leu-51. |
| 522632 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 426 as residues: Cys-69 to Asn-74, Lys-83 to Gly-89. |
| 524655 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 427 as residues: Tyr-28 to Asn-35, Ile-45 to Lys-55. |
| 525847 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 428 as residues: Lys-27 to Asp-33. |
| 530306 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 429 as residues: Arg-1 to Arg-11, Tyr-21 to His-27. |
| 532818 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 430 as residues: Pro-10 to Thr-21, Asp-32 to Thr-38, Gly-47 to Glu-60. |
| 533385 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 431 as residues: Asn-17 to Trp-22, Pro-34 to Glu-49, His-61 to Ser-71. |
| 533532 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 432 as residues: Glu-29 to Lys-37, Lys-110 to Ile-118, Arg-126 to Cys-135, Lys-157 to Gly-163, Gln-188 to Trp-201, Glu-269 to Thr-278. |
| 534852 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 433 as residues: Gln-1 to Ser-14, Thr-23 to Val-31, Cys-43 to Ala-56, Glu-58 to Ser-96, Gly-101 to Tyr-109, Asn-143 to Tyr-148, Pro-154 to His-164, Ser-195 to Asn-201, Pro-264 to Pro-271. |
| 537910 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 434 as residues: Pro-4 to Ala-11, Pro-110 to Arg-122. |
| 539577 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 436 as residues: Pro-9 to Gln-19. |
| 548595 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 439 as residues: Asp-27 to Asp-33, His-54 to Tyr-59, Ile-91 to Pro-96. |
| 549337 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 440 as residues: Pro-38 to Asp-43, Arg-155 to Phe-162, Pro-164 to Asp-170, Pro-172 to Gly-182. |
| 553091 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 442 as residues: Lys-55 to Lys-62, Gln-67 to Val-76, Lys-101 to Glu-111, Lys-125 to Arg-140, Arg-161 to Arg-166, Gln-171 to Asp-187. |
| 553827 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 443 as residues: Glu-17 to Pro-22, Pro-70 to His-76, Thr-84 to Arg-92, Asp-109 to Tyr-117. |
| 556350 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 444 as residues: Glu-1 to Ser-15, Phe-17 to Pro-22, Lys-116 to Arg-131. |
| 556351 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 445 as residues: Gln-9 to Phe-23, Cys-53 to Ser-64, Glu-86 to Asp-93, Ile-100 to Glu-112, Tyr-124 to Glu-133, Ser-197 to Ser-204, Asn-208 to Glu-214, Lys-228 to Lys-233, Tyr-248 to Lys-259, Pro-330 to Ala-335, Gln-349 to Lys-355, Ala-365 to Glu-374, Ser-376 to Ser-397. |
| 557007 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 446 as residues: Pro-46 to Tyr-54, Pro-81 to Gly-87, Pro-97 to Gly-104, Leu-106 to Asn-116, Asn-129 to Phe-134, Lys-147 to Tyr-158, Ala-192 to Ser-199, Asp-204 to Glu-215, Gly-221 to Ser-232. |
| 558456 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 448 as |

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| | residues: Glu-19 to Tyr-24, Ser-60 to Thr-65, Thr-82 to Pro-88. |
| 558708 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 449 as residues: Arg-13 to Ala-20, Pro-27 to Arg-32, Lys-37 to Glu-62. |
| 574789 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 450 as residues: Gly-16 to Lys-21. |
| 578203 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 451 as residues: Thr-7 to Arg-18. |
| 588869 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 453 as residues: Pro-14 to Ser-19, Glu-55 to Phe-60, Asp-93 to Ser-98, Thr-138 to Tyr-144, Asn-155 to Phe-163, Arg-168 to Ser-175, Gln-205 to Lys-210, Phe-226 to Thr-233. |
| 597076 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 454 as residues: Ser-50 to Gln-56. |
| 598656 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 455 as residues: Ser-85 to Tyr-92, Arg-109 to Lys-114. |
| 614329 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 457 as residues: Arg-59 to Ala-67, Asn-78 to Arg-85. |
| 620956 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 459 as residues: Ala-11 to Gln-16. |
| 621889 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 460 as residues: Ser-84 to Gly-99, Pro-101 to Ser-112. |
| 651784 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 462 as residues: Gly-29 to Gly-35, Ala-37 to Ala-48. |
| 651826 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 463 as residues: Arg-1 to Ser-16, Gln-49 to Lys-60, Glu-77 to Leu-83, Gln-91 to Arg-100, Phe-140 to Ala-154, Asp-214 to Leu-219, Ala-258 to Met-275, Ile-289 to Lys-295, Ala-314 to Glu-320, Arg-327 to Met-332, Thr-383 to Ser-388, Ser-425 to Asp-433. |
| 653282 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 464 as residues: Arg-12 to Ile-19, Glu-23 to Pro-29, Pro-37 to Val-45. |
| 657122 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 465 as residues: Ala-6 to Gly-13, Arg-41 to Thr-47. |
| 661442 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 466 as residues: Arg-6 to Ser-11, Asp-53 to Ser-59, Ala-88 to Ala-104, Thr-114 to Asn-121, Glu-128 to Val-137, Asn-144 to Thr-150, Ser-174 to Asn-180, Gly-203 to Asp-212. |
| 664914 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 467 as residues: Pro-12 to Lys-17. |
| 666654 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 468 as residues: Thr-5 to Leu-10, Pro-13 to Leu-24. |
| 667084 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 469 as residues: Pro-1 to Pro-9, Gly-50 to Ser-55, Gly-80 to Ser-85, Gly-91 to Tyr-96, Arg-144 to Gln-160, Asp-195 to Thr-202, Lys-246 to Glu-252, Met-283 to Glu-288, Glu-292 to Glu-299, Ser-304 to Asn-310, Ala-356 to Tyr-362, Met-387 to Tyr-394, Gln-424 to Thr-431, Ser-450 to Arg-459. |
| 667380 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 470 as residues: Pro-1 to Pro-6, Thr-134 to Gln-140, Tyr-142 to Arg-150. |
| 671315 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 472 as residues: Ala-16 to Gly-21, Glu-28 to Gly-35. |
| 671993 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 473 as residues: Pro-8 to Ser-23. |
| 674618 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 474 as residues: Ile-3 to Ser-11, Arg-24 to Glu-30. |
| 675027 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 475 as residues: His-47 to Ile-52, Ala-71 to Arg-76, Asp-78 to Lys-87. |
| 677202 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 476 as residues: Val-45 to Gly-50, Thr-56 to Glu-64. |
| 678504 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 477 as residues: Arg-7 to Ser-19. |

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| 678985 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 478 as residues: Lys-17 to Thr-23, Leu-26 to His-36, His-41 to Pro-56, Ala-60 to Gly-71, Lys-77 to Ser-91, Asp-101 to Lys-109, Asp-200 to Gly-206, Asp-245 to Leu-253, Gln-262 to Phe-274. |
| 682161 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 479 as residues: Arg-5 to Pro-11, Pro-22 to Thr-29, Trp-53 to Arg-62, Pro-69 to Gly-78, Lys-98 to Tyr-103, Glu-144 to His-151, Pro-172 to Leu-178, Gln-193 to Glu-200. |
| 683476 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 480 as residues: Ala-5 to Trp-19. |
| 693589 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 482 as residues: Cys-1 to Arg-13, Pro-15 to Gly-21, Gly-54 to Ser-59, Trp-73 to Lys-78, Ser-90 to Arg-104. |
| 694991 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 483 as residues: Lys-1 to Thr-6, Pro-8 to Gly-19, Val-61 to Arg-66. |
| 698669 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 485 as residues: Pro-31 to His-36, Gly-43 to Tyr-48, Glu-136 to Ser-142, Pro-178 to Arg-183, Pro-273 to Asp-278, Gly-318 to Cys-326. |
| 707357 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 488 as residues: Gly-6 to Arg-21, Arg-89 to Asp-94. |
| 707360 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 489 as residues: Ser-13 to Glu-26, Ser-48 to Val-55, Lys-85 to Thr-91, Asp-115 to Trp-120. |
| 707375 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 490 as residues: Arg-1 to Gly-6, Ala-12 to Arg-19, Arg-34 to Arg-40, Arg-47 to Ala-58, Ser-67 to Thr-80, Ser-109 to Ser-117, Asn-134 to Ser-141, Pro-175 to Arg-181, Lys-212 to Thr-218, Asp-275 to Cys-285. |
| 707754 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 491 as residues: Val-32 to Leu-41, Asn-55 to Arg-63, Pro-104 to Ala-113. |
| 712248 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 493 as residues: Ser-13 to Gly-20, Gln-36 to Ser-41, Pro-44 to Phe-58. |
| 715445 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 494 as residues: Gly-23 to Thr-29, Ser-32 to Val-40, Lys-181 to Ser-188, Glu-197 to Gln-204, Arg-244 to His-249, Ala-253 to Thr-264. |
| 716362 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 495 as residues: Cys-1 to Gly-8, Arg-71 to Ser-77, His-102 to Ser-108. |
| 716835 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 496 as residues: Gln-7 to Glu-14, Ala-24 to Arg-41. |
| 717685 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 498 as residues: Gly-1 to Ala-7, His-70 to Gly-76, Gln-130 to Thr-135, Thr-182 to Pro-189, Asn-259 to Leu-267, Glu-280 to Ala-289, Gln-303 to Asn-310. |
| 719755 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 499 as residues: Asp-14 to Pro-25, Pro-59 to Glu-100, Cys-126 to Gly-145, Pro-158 to Lys-164, Lys-176 to Leu-197, Leu-221 to Tyr-238. |
| 720389 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 500 as residues: Thr-13 to Ala-19, Ala-26 to Pro-36, Ser-63 to Gly-68. |
| 720903 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 501 as residues: Asn-6 to Ser-11, Ala-91 to Arg-99, Trp-107 to Tyr-113, Tyr-131 to Met-137, Asp-150 to Val-157. |
| 721562 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 503 as residues: Asp-39 to Ile-45. |
| 722775 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 504 as residues: Pro-34 to Ser-41, Cys-49 to Arg-55, Thr-92 to Ala-98, Thr-160 to Gly-173, Thr-194 to Pro-200, Gly-274 to Trp-282, Pro-285 to Ala-291. |
| 724463 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 505 as residues: Glu-9 to Lys-15, Pro-23 to Tyr-33. |
| 728418 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 507 as residues: Ala-6 to Gln-11, Ser-25 to Ser-30, Lys-63 to Gly-69, Ser-108 to Asp-118, Arg- |

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| | 127 to His-132, Asp-156 to Cys-161. |
| 728920 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 508 as residues: Thr-7 to Ala-15. |
| 732958 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 509 as residues: Thr-10 to Ala-15, Pro-63 to Ser-78, Ser-82 to Leu-94. |
| 733134 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 510 as residues: Arg-4 to Gly-24, Lys-47 to Phe-55, Lys-61 to Ala-67, Gly-108 to Thr-114, Pro-184 to Pro-191, Pro-292 to Arg-299, Pro-355 to Glu-392. |
| 734099 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 511 as residues: His-1 to Arg-7, Gln-15 to Ala-23, Met-43 to Gln-55. |
| 738911 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 515 as residues: Arg-4 to Asp-10, Ser-64 to His-75, Pro-127 to Asn-136, Phe-143 to Gln-150. |
| 739226 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 516 as residues: Asn-1 to Thr-7. |
| 739527 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 517 as residues: Gly-1 to Arg-9, Val-28 to Gly-39, Asp-52 to Leu-60, Ala-106 to Trp-117. |
| 744331 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 520 as residues: Ser-17 to Arg-24. |
| 744751 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 521 as residues: Ser-8 to Val-13, Pro-34 to Cys-40, Tyr-48 to Ser-55, Gly-63 to Ser-73. |
| 745750 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 522 as residues: Ser-2 to Glu-17. |
| 746285 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 523 as residues: Lys-87 to Lys-92. |
| 746416 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 524 as residues: Arg-6 to Leu-12, Tyr-18 to Asp-25. |
| 747851 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 525 as residues: Gly-124 to Ser-129, Leu-162 to Gly-167, Val-272 to Ala-278, Lys-293 to Asp-298. |
| 751315 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 527 as residues: Cys-12 to Pro-20. |
| 754634 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 529 as residues: Asp-1 to Thr-10. |
| 756833 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 531 as residues: Thr-36 to Pro-49, Glu-52 to Pro-67. |
| 756878 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 532 as residues: Pro-8 to Lys-15, Gly-69 to Trp-75. |
| 757332 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 533 as residues: Gln-23 to Val-31, Phe-39 to Ile-52. |
| 760835 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 534 as residues: Phe-1 to Lys-7, Cys-82 to Ser-90. |
| 761760 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 535 as residues: Arg-34 to Pro-39, Gly-43 to Asp-51, Gln-147 to Arg-153. |
| 762520 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 536 as residues: His-6 to His-11, Ala-13 to Glu-18, Ala-60 to Ser-65, Ile-72 to Ser-77, Gln-95 to Phe-101, Leu-136 to Ser-142. |
| 764461 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 537 as residues: Val-15 to Ala-22, Val-26 to Gly-38. |
| 764517 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 538 as residues: Gly-30 to Lys-36, Gly-94 to Ala-100, Gln-150 to Gly-156, Gln-189 to Leu-195. |
| 765132 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 539 as residues: Asn-80 to Thr-87, Ser-165 to Leu-182, Thr-196 to His-201, Lys-271 to His-279, Asp-286 to Gly-292, Tyr-294 to Leu-302. |
| 765667 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 540 as residues: Pro-14 to Pro-21, Pro-30 to Pro-36. |

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| 767113 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 541 as residues: Ala-62 to Pro-13, Pro-75 to Thr-83, Thr-110 to Phe-115, Glu-142 to Asp-150, Gln-158 to Ser-167, Glu-182 to Thr-187, Ser-190 to Asp-204. |
| 767204 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 542 as residues: Ala-22 to Met-29, Arg-45 to Phe-56, Asp-63 to Asp-71, Gly-81 to Ala-88, Gln-155 to Trp-162. |
| 767962 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 544 as residues: Glu-126 to Gly-132, Asn-146 to Ser-158, Phe-179 to Leu-188. |
| 768040 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 545 as residues: Pro-24 to Trp-32, Val-51 to Arg-62, Gly-84 to Asp-93, Asp-108 to Asn-120, Glu-150 to Val-158, Gly-169 to Gly-175. |
| 769956 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 546 as residues: Pro-1 to Arg-6. |
| 770133 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 547 as residues: Glu-1 to Ser-6. |
| 771964 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 549 as residues: Pro-8 to Gly-15, Thr-26 to Phe-32, Thr-102 to Ser-109, Ala-112 to Thr-118, His-130 to Glu-152, Ser-161 to Ala-170, Ser-204 to His-209, Gly-221 to Ser-229, Ser-233 to Ala-240, Glu-242 to Pro-247, Leu-251 to Gln-258, Leu-278 to Leu-285, Thr-333 to Glu-338. |
| 773387 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 551 as residues: Lys-36 to Lys-45, Ala-59 to Arg-67, Cys-99 to Arg-108, Ala-115 to Cys-125, Arg-143 to Arg-153. |
| 773827 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 552 as residues: Pro-1 to Ala-15, Ser-72 to His-79, Gly-89 to Tyr-105, Lys-179 to Lys-184, Arg-246 to Asp-251, Glu-302 to Lys-309, Ser-329 to Phe-341. |
| 774108 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 553 as residues: Ala-1 to Gly-21, Pro-28 to Leu-39, Pro-48 to Asp-62, Arg-71 to Arg-78. |
| 775339 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 555 as residues: Asp-6 to Thr-13, Asp-24 to Met-30. |
| 775582 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 556 as residues: Gly-1 to Asn-12, Ser-69 to Glu-77. |
| 777809 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 558 as residues: Arg-15 to Gly-25. |
| 778927 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 559 as residues: Ala-74 to Ser-82, Asn-109 to Ala-124, Ser-147 to Ile-152, Pro-188 to Gly-194, Arg-290 to Pro-299, Tyr-307 to Glu-319, Tyr-341 to Ile-346, Lys-423 to Ser-441, Gln-452 to Glu-465. |
| 779262 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 560 as residues: Arg-5 to Ile-24, Gly-35 to Trp-40, Glu-42 to Thr-48, Lys-76 to Gly-95. |
| 780149 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 562 as residues: Gly-13 to Gln-18, Pro-71 to Glu-89, Ile-134 to Asp-139, Pro-232 to Met-240. |
| 780583 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 563 as residues: Asn-58 to Thr-64, Ile-72 to Ser-78, Gly-119 to Lys-128. |
| 780960 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 564 as residues: Ala-7 to Ile-14, Lys-27 to Asp-35, Thr-63 to Leu-73. |
| 781469 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 565 as residues: Pro-1 to Ala-12, Arg-27 to Gln-45, Arg-57 to Gln-64, Lys-74 to Asp-96. |
| 781771 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 567 as residues: Glu-38 to Leu-52, Glu-64 to Lys-72, Asn-92 to Ala-102, Ala-104 to Asp-119, Pro-121 to Pro-130, Ser-165 to Ser-173. |
| 782033 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 568 as residues: Ala-1 to Gly-19, Gln-41 to Gly-46. |
| 782105 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 569 as residues: Leu-13 to Gly-34, Arg-77 to Pro-85, Lys-129 to Arg-135. |
| 782122 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 570 as |

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| | residues: Pro-1 to Arg-6, Ala-102 to Ala-108, Pro-148 to Asp-158, Gly-164 to Ala-171, Pro-223 to Asn-231, Pro-272 to Ser-282, Ala-294 to Pro-310, Pro-322 to Arg-327. |
| 783245 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 572 as residues: Leu-90 to Arg-97, Ala-107 to Pro-113. |
| 783247 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 573 as residues: Ser-2 to Leu-8. |
| 783413 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 574 as residues: Lys-33 to Val-39. |
| 784407 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 575 as residues: Gly-28 to Val-36. |
| 784548 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 576 as residues: Trp-1 to Pro-9, Pro-15 to Gln-24, Pro-52 to Thr-57. |
| 785677 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 578 as residues: Gly-7 to Gly-14. |
| 786238 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 579 as residues: Gly-1 to Gly-8. |
| 786389 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 580 as residues: Ser-2 to Arg-16, Gly-34 to Glu-44, Arg-62 to Gln-69, Pro-102 to Ile-108, Asp-187 to Thr-193, Leu-203 to Pro-213. |
| 786929 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 581 as residues: Pro-2 to Trp-7, Tyr-36 to Tyr-43. |
| 786932 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 582 as residues: Ser-18 to His-30, Thr-39 to Arg-51, Leu-59 to Thr-66, Pro-131 to Lys-136, Pro-149 to Ser-157. |
| 787078 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 583 as residues: Glu-20 to Pro-26. |
| 787283 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 585 as residues: Glu-7 to Arg-13, Gln-26 to Arg-34. |
| 788988 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 587 as residues: Pro-41 to Tyr-50, Thr-70 to Lys-75. |
| 789092 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 588 as residues: Thr-27 to Ala-34, Leu-41 to Glu-48, Glu-76 to Asn-87, Asn-110 to Leu-118, Gly-125 to Lys-133. |
| 789298 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 589 as residues: Arg-1 to Ser-14, Glu-56 to Gly-61, Ala-92 to Gln-98, Glu-134 to Val-154. |
| 789718 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 591 as residues: Cys-17 to Ala-24. |
| 790285 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 594 as residues: Thr-11 to Leu-18, Leu-22 to Val-31, Trp-33 to Lys-49, Ser-63 to Glu-72, Cys-80 to Ala-91, Pro-97 to His-116. |
| 790509 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 595 as residues: Ser-6 to His-20, Leu-22 to Gly-32, Lys-103 to Arg-111, Ser-125 to Gly-130, Glu-204 to His-210, Thr-213 to His-219, Pro-222 to Asp-244, Ser-250 to Glu-258, Arg-263 to Arg-268. |
| 790775 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 596 as residues: Arg-42 to Asp-48, Cys-79 to Thr-85, Leu-113 to Ser-123. |
| 790888 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 597 as residues: Pro-14 to Asp-19, Asp-40 to Leu-45, Ser-53 to Val-58, Leu-81 to Tyr-91. |
| 791506 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 598 as residues: Arg-1 to Gly-9, Asp-19 to His-25, Gly-51 to Glu-61. |
| 792002 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 601 as residues: Arg-1 to Gly-6, Val-22 to Pro-35, Val-106 to Ile-112, His-118 to Gln-124, Ser-132 to Leu-145, Asn-164 to Asn-170, Arg-187 to Tyr-192. |
| 792291 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 602 as residues: Pro-14 to Arg-31. |
| 792371 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 603 as |

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| | residues: Gly-37 to Gly-52, Pro-63 to Gly-69, Ser-74 to His-81, Ser-94 to Thr-105, Val-109 to Thr-114, Phe-165 to Ser-181, Ala-191 to Asp-196, Asn-209 to Ser-216. |
| 792660 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 604 as residues: Thr-11 to Arg-16, Asn-78 to Asp-84. |
| 792782 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 605 as residues: Ala-65 to Gly-81. |
| 792890 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 606 as residues: Pro-26 to His-31, Arg-34 to Ser-44, Pro-59 to Ser-71, Leu-77 to Gly-83. |
| 792931 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 607 as residues: Pro-3 to His-12. |
| 792943 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 608 as residues: Lys-3 to Tyr-9, Gly-15 to Thr-22, Leu-36 to Asp-41, Leu-67 to Lys-76, Asp-86 to Ser-93, Tyr-174 to Asp-184, Leu-255 to Glu-260, Ile-331 to Val-337. |
| 793446 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 611 as residues: His-1 to Gly-12. |
| 793639 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 612 as residues: Arg-6 to Arg-13, Pro-47 to Val-52, Gln-57 to Arg-65, Arg-72 to Glu-78, Asp-117 to Thr-124, Phe-132 to His-137. |
| 794213 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 613 as residues: Tyr-1 to Trp-9, Thr-44 to Leu-49. |
| 795955 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 615 as residues: Lys-60 to Lys-65, Lys-99 to Ala-104. |
| 796555 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 617 as residues: Ser-1 to Gly-10, Gly-90 to Gly-97, Asn-185 to Arg-197, Pro-202 to Arg-211. |
| 796675 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 618 as residues: Ser-35 to Gly-40, Ser-103 to His-109, Tyr-151 to Gly-159, Pro-216 to Glu-224, Asn-249 to Trp-258, Pro-278 to Glu-284. |
| 796743 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 619 as residues: Asn-1 to Gly-6, Asn-100 to Glu-106, Gln-108 to Asp-116, Asp-146 to Thr-151, Thr-191 to Glu-198. |
| 796792 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 620 as residues: Asn-23 to Gly-28, Cys-41 to Asp-47, Gln-82 to Glu-88. |
| 799668 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 621 as residues: Gly-2 to Arg-10, Ile-27 to Pro-33. |
| 799669 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 622 as residues: Gly-1 to Ser-12. |
| 799673 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 623 as residues: Gly-1 to Ala-14, Leu-38 to Pro-46. |
| 799674 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 624 as residues: Pro-39 to Pro-45. |
| 799678 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 625 as residues: Lys-54 to Ser-60, Tyr-86 to His-93. |
| 799728 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 626 as residues: Trp-7 to Gln-19. |
| 799748 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 627 as residues: Glu-7 to Arg-12, Lys-62 to His-68. |
| 799760 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 628 as residues: Ile-15 to Trp-22. |
| 800296 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 630 as residues: Asn-19 to Thr-39, Glu-42 to Ile-48, Arg-55 to Asp-66, Ile-130 to Arg-135, Lys-149 to Ala-156, Glu-166 to Leu-176, Met-213 to Lys-219, Pro-233 to Pro-248, Lys-258 to Lys-263. |
| 800327 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 631 as residues: Arg-13 to Gly-19, Lys-32 to Glu-39, Lys-94 to Trp-100, Asn-102 to Asp-108, Ala-117 to Leu-129. |
| 800816 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 632 as |

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| | residues: Lys-1 to Ile-11, Gln-36 to Leu-46. |
| 800835 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 633 as residues: Trp-1 to Gln-11, Gly-37 to Gln-50, Ser-109 to Gln-114, Glu-146 to Leu-155, Glu-175 to Gly-180, Thr-188 to Ser-200. |
| 805429 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 634 as residues: Pro-6 to Ser-51, Gln-100 to Glu-107. |
| 805458 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 635 as residues: Glu-57 to Ser-62, Thr-102 to Ser-120. |
| 805478 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 636 as residues: Glu-31 to Glu-37, Pro-47 to Ser-52, Asn-57 to Asn-66. |
| 805805 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 637 as residues: Arg-1 to Cys-16, Tyr-59 to Lys-68, Glu-76 to Arg-82. |
| 806486 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 638 as residues: Phe-1 to Val-6, Pro-11 to Gly-18. |
| 806498 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 639 as residues: Pro-6 to Ser-17, Arg-81 to Thr-88, Arg-198 to Val-203, Arg-285 to Arg-296, Gln-302 to Ser-361, Leu-399 to Ser-407. |
| 810870 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 641 as residues: Val-12 to Ile-21. |
| 811730 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 642 as residues: Arg-33 to Arg-40. |
| 813262 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 645 as residues: Gly-31 to Asp-51, Cys-68 to Val-81, Leu-85 to Cys-92. |
| 815637 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 646 as residues: Arg-13 to Asp-19, Ser-80 to Gly-91, Pro-99 to Ser-111. |
| 815853 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 647 as residues: Cys-25 to Ser-31, Gln-63 to Asp-73, Arg-98 to Gly-106, Pro-120 to Arg-125, Leu-136 to Asp-141, Gly-155 to Glu-170, Phe-179 to Gly-186. |
| 815999 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 648 as residues: Asp-1 to Asp-10, Arg-19 to Glu-28, Gly-86 to Leu-93, Arg-113 to His-118. |
| 823427 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 649 as residues: Pro-16 to Cys-27, Arg-70 to Arg-76. |
| 823704 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 650 as residues: Val-29 to Lys-34, Arg-58 to His-63, Gln-87 to Lys-97, Arg-195 to Ser-200. |
| 824798 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 651 as residues: Thr-28 to His-34. |
| 825018 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 652 as residues: Gln-1 to Asn-11, Leu-19 to Thr-24, Lys-47 to Arg-55, Lys-94 to Asp-99, Ala-101 to Arg-107, Ala-137 to Tyr-146, Gln-150 to Ser-163, Gly-169 to Lys-175, Thr-182 to Ala-189, Glu-249 to Ser-258, Pro-266 to Tyr-275, Tyr-285 to Gly-298, Asp-302 to Gln-315, Tyr-318 to Thr-325, Gln-332 to Ala-359, Ser-372 to Phe-384, Leu-390 to Ala-399, Ala-428 to Arg-437. |
| 825787 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 654 as residues: Pro-21 to Leu-28, Arg-40 to Ile-49, Asp-84 to Asn-93, Arg-124 to Asn-130, Gly-140 to Asn-145, Leu-187 to Gln-196, Pro-208 to Asp-213, Arg-244 to Asp-252, Ile-325 to Gln-336, Glu-372 to Ala-379, Asn-435 to Leu-446, Ala-460 to Arg-467, Val-500 to Asp-506, Lys-524 to Asn-533, Thr-592 to Lys-598, Asp-648 to Ser-656. |
| 826116 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 655 as residues: Glu-20 to Cys-35. |
| 826147 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 656 as residues: Lys-18 to Leu-24. |
| 827586 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 658 as residues: Ser-7 to Gly-14, Leu-22 to Ala-28, Thr-57 to Ser-62. |
| 827735 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 660 as residues: Pro-2 to Ser-12, Gln-25 to Glu-31, Val-40 to Arg-45. |
| 827740 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 661 as |

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| | residues: Ile-22 to Lys-28. |
| 827808 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 662 as residues: Glu-2 to Gln-13, Gln-20 to Gly-29, Arg-32 to Cys-47, Pro-54 to Trp-61, Thr-73 to Gln-91, Gly-96 to Ser-103. |
| 828357 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 664 as residues: Gly-1 to Gly-10, Val-25 to Glu-32, His-67 to Arg-73. |
| 828612 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 666 as residues: Asp-25 to Gln-31, Asp-36 to Tyr-41, Gln-43 to Thr-48, Lys-71 to Thr-76. |
| 828647 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 667 as residues: Ser-2 to Ser-8, Arg-61 to Gln-74, Ser-192 to Asn-202, Gln-229 to Lys-236, Gly-281 to Gly-292, Glu-333 to Ala-345, Ala-352 to Gln-358, Glu-360 to Leu-366, Asp-443 to Ser-449, Glu-452 to Glu-459, Asp-485 to Thr-492, Ala-510 to Gln-516, Ala-545 to Ala-552, Leu-560 to Thr-566, Glu-586 to Ala-592, Asp-601 to Gln-607, Leu-609 to Leu-620. |
| 828698 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 668 as residues: Pro-28 to Ser-43, Pro-45 to Ala-50, His-58 to Gln-63. |
| 828962 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 669 as residues: Ala-42 to Gly-49, Thr-54 to Cys-63. |
| 829282 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 671 as residues: Ser-7 to Gln-12, Gly-25 to Gly-31, Gly-71 to Gly-84, Leu-147 to Glu-164, Trp-172 to Leu-180. |
| 829368 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 672 as residues: Glu-1 to Tyr-7, Pro-13 to Glu-24, Arg-31 to Ile-39, Gln-59 to Lys-65, His-67 to Leu-74. |
| 829751 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 673 as residues: Ala-29 to Arg-45, Ser-48 to Glu-59, Lys-73 to Trp-79, Ala-100 to Ser-109. |
| 829934 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 675 as residues: Arg-1 to Arg-6, Ser-46 to Asp-71, Glu-76 to Glu-90, Gln-107 to Tyr-118, Ser-124 to Asp-131, Glu-163 to Asp-170, Ala-239 to Asp-245, Asp-262 to Arg-268, Gln-276 to Asp-283, Arg-293 to Lys-300, Ser-307 to Glu-313, Phe-346 to Phe-351, Phe-361 to Ala-373. |
| 829951 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 677 as residues: Thr-21 to Lys-28. |
| 830173 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 678 as residues: Gly-51 to Asn-68, Thr-75 to Lys-82, Ala-86 to Ala-97, Asn-99 to Arg-106, Leu-121 to Phe-126, Ala-155 to Ser-163, Asp-175 to Asp-180, Ala-184 to Phe-196, Leu-204 to Asn-214, Asp-219 to Gln-232, Leu-269 to Arg-274, Pro-392 to Pro-400, Thr-430 to Asn-437, Tyr-472 to Gln-477, Leu-483 to Gln-499, Asn-516 to Gln-524, Ser-533 to Gln-546, Lys-562 to Glu-576, Leu-589 to Ala-594, Asp-624 to Ala-633, Ile-741 to Asp-746, Val-817 to Lys-839, Tyr-872 to Lys-878, Thr-929 to Asp-940. |
| 830365 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 680 as residues: Trp-36 to Glu-41, Asp-71 to Arg-76, Asn-80 to Gly-87, Arg-103 to Pro-115. |
| 830456 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 681 as residues: Leu-48 to Cys-54. |
| 830549 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 682 as residues: Ser-1 to Pro-24, Pro-40 to Thr-50, Glu-62 to Gly-83, Arg-103 to Leu-108, Ser-141 to Lys-146, Lys-184 to Ser-190. |
| 830602 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 683 as residues: Arg-53 to Thr-63, Ile-100 to Lys-108. |
| 830610 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 684 as residues: Pro-27 to Cys-32, Ala-61 to Gly-70, Pro-76 to Gly-85, Met-115 to Gly-120, Glu-162 to Lys-171, Pro-222 to Tyr-228, Glu-242 to Thr-248, Lys-261 to Gly-269. |
| 830644 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 685 as residues: Ile-1 to Ser-10. |
| 830707 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 686 as residues: Asn-34 to Leu-53, Gln-61 to Leu-67. |

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| 830709 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 687 as residues: Arg-13 to Gln-18, Pro-22 to Ala-40, Ala-66 to Asp-84, Glu-94 to Arg-101. |
| 830733 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 688 as residues: Glu-1 to Asp-8. |
| 830855 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 690 as residues: Ser-1 to His-6. |
| 830949 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 691 as residues: Arg-5 to Arg-12, Gly-25 to Trp-30, Thr-77 to Trp-96, Thr-101 to Glu-106, Gly-109 to Arg-127. |
| 830965 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 692 as residues: Leu-24 to Arg-56, Pro-83 to Arg-90, Ile-110 to Ile-115, Lys-123 to Val-136. |
| 830973 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 693 as residues: Ser-1 to Asn-7, Tyr-13 to Asp-23. |
| 830989 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 695 as residues: Cys-2 to Ser-16, Glu-55 to Lys-61, Pro-83 to Leu-88, Ser-135 to Pro-148, Val-152 to Arg-163, Pro-223 to Thr-230, Ala-242 to Val-253, Arg-258 to Glu-274, Gly-290 to Asp-300, Lys-337 to Asn-345, Asp-373 to Ala-398, Gly-401 to Lys-406, Gln-410 to Ala-430, Pro-433 to Gln-460. |
| 831134 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 696 as residues: Ala-19 to His-24. |
| 831200 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 697 as residues: Trp-1 to Gly-6. |
| 831531 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 699 as residues: Ser-94 to Asn-116, Glu-139 to Asp-155, Tyr-190 to Leu-195, Ile-230 to Ile-235, Ser-309 to Glu-317. |
| 831665 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 700 as residues: Leu-4 to Trp-12. |
| 831724 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 701 as residues: Pro-26 to Lys-32. |
| 831884 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 702 as residues: Pro-46 to Ala-52, Thr-68 to Trp-86, Arg-91 to Arg-96, Lys-127 to Asp-141. |
| 831897 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 703 as residues: Pro-10 to Ser-20, Val-73 to Ser-78, Asp-123 to Glu-134, Leu-138 to Val-149, Ala-181 to Ala-187, Thr-189 to Val-196, Arg-213 to Gln-224. |
| 831922 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 704 as residues: Leu-32 to Asp-37, Ile-43 to Asn-49. |
| 832266 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 707 as residues: Ala-73 to Arg-79. |
| 832309 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 708 as residues: Val-10 to Gly-15, Ser-98 to Thr-105. |
| 832342 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 709 as residues: Pro-9 to Trp-16, Thr-66 to Ser-72. |
| 832351 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 710 as residues: Asp-16 to Val-21, Leu-54 to Asp-71. |
| 832352 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 711 as residues: Asp-16 to Val-21, Leu-33 to Asp-50. |
| 832434 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 712 as residues: Tyr-15 to Glu-23, Ser-46 to Arg-51, Gln-56 to Trp-61, Pro-79 to Lys-86. |
| 832490 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 713 as residues: Arg-16 to Gly-23, Ala-37 to Asp-46, Asp-91 to Asp-97. |
| 832573 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 714 as residues: Ala-9 to Gln-16, Glu-21 to Arg-27, Gly-66 to Pro-72. |
| 833394 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 716 as residues: Glu-1 to Gly-6, Asp-12 to Gly-22, Ile-28 to Gln-33, Cys-86 to Gly-92, Gly-96 to Ile-105. |
| 835355 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 717 as |

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| | residues: Glu-8 to Ser-15, Gly-42 to Leu-49, Pro-73 to Gly-79, Tyr-82 to Arg-87, Ser-109 to Gly-118, Glu-122 to Ile-128, Asp-132 to Gly-137, Asp-146 to Arg-151, Pro-153 to Lys-158, Gly-191 to His-197, Tyr-210 to Ser-218, Lys-234 to Gly-239, Ala-246 to Ala-252, His-257 to Pro-268, Ser-274 to Gly-280, Pro-316 to Tyr-323, Ile-358 to Leu-363, Gln-375 to Tyr-381, Gln-390 to Tyr-397, Gln-418 to Cys-430. |
| 835497 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 718 as residues: Glu-141 to Pro-151, Asp-179 to Glu-184, Gly-214 to Ser-219, Thr-226 to Tyr-231, Thr-239 to Gly-248, Pro-281 to Gly-297, Pro-326 to Arg-336, Gln-408 to Asp-416. |
| 835978 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 720 as residues: Trp-25 to Val-31. |
| 836274 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 722 as residues: Ser-1 to Glu-9. |
| 836731 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 723 as residues: Lys-15 to Glu-22, Gly-25 to Ala-34, Glu-75 to Gly-81, Gln-91 to Val-100, Pro-146 to Glu-155, Gln-161 to Phe-167, Asn-170 to Gly-178. |
| 838014 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 724 as residues: Arg-1 to Pro-10, Asp-170 to Pro-176, Arg-203 to Tyr-212, Gly-228 to Lys-235. |
| 838874 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 725 as residues: Gln-30 to Gln-45. |
| 839120 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 726 as residues: Thr-22 to Arg-27, Arg-69 to Gly-75, Leu-77 to Pro-85. |
| 839611 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 727 as residues: Asp-12 to Thr-17. |
| 840138 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 728 as residues: Ser-1 to Thr-10. |
| 840616 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 729 as residues: Lys-93 to Gly-99, Glu-144 to Leu-160, Ser-265 to Asp-270, Thr-382 to Gln-396, Val-512 to Val-517, Glu-519 to Asp-535. |
| 840780 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 730 as residues: Leu-8 to Gly-14, Pro-151 to Glu-157. |
| 840857 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 731 as residues: Gln-7 to Glu-22, Ala-27 to Arg-46, Ser-138 to Lys-147, Lys-158 to Pro-163, Asn-171 to Glu-187, Glu-202 to Val-208, Glu-234 to Gly-240, Ser-253 to Lys-260, Gln-272 to Pro-279, Arg-292 to Glu-307, Arg-310 to Arg-317, Asp-342 to Gly-351, Pro-367 to Gly-375, Pro-378 to Arg-388, Leu-425 to Ala-447, Arg-536 to Asp-544, Lys-551 to Lys-561, Val-599 to Asp-604, Ser-622 to Ala-630, Pro-653 to Phe-659, Thr-666 to Ile-673, Pro-699 to Phe-705, Asn-709 to Gly-719, Ala-725 to Phe-737. |
| 840862 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 732 as residues: Arg-2 to Pro-12, Lys-32 to Asn-37, His-75 to Asn-82. |
| 840864 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 733 as residues: Pro-17 to Arg-30, Cys-34 to Gly-40, Met-74 to Glu-81, Pro-106 to Asp-111, Val-136 to Cys-147, Asn-192 to Asp-198. |
| 840938 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 735 as residues: Ser-140 to Thr-148, Thr-194 to Lys-202. |
| 841884 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 736 as residues: Thr-34 to Glu-47. |
| 842241 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 737 as residues: Thr-92 to Lys-101, Glu-134 to Thr-142, Glu-149 to Lys-155, Trp-179 to Ser-187, Thr-205 to Arg-211, Ser-218 to Tyr-225, Asp-283 to Gln-290, Glu-292 to Ile-302, Asn-304 to Met-315. |
| 843712 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 738 as residues: Arg-10 to Asn-16, Ala-59 to Pro-67. |
| 844040 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 739 as residues: Phe-59 to Glu-68, Lys-105 to Gly-111. |
| 844617 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 742 as |

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| | residues: Arg-1 to Lys-7. |
| 846187 | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 745 as residues: Gly-8 to Gly-14, Gly-41 to Glu-48, Glu-54 to Lys-74, Glu-87 to Arg-98, Thr-158 to Asn-166, Gly-247 to Ser-254, Gly-257 to Arg-277, Ala-437 to Ser-444, Lys-505 to Arg-510, Phe-519 to Tyr-525, Lys-531 to Pro-538, Gly-562 to Leu-571, Phe-606 to Val-613, Val-692 to Ala-697, Ser-705 to Leu-715, Leu-742 to Cys-747. |
| HANGA53R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 749 as residues: Arg-4 to Ser-9. |
| HAHCP93R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 752 as residues: Ser-1 to Ser-12, Thr-23 to Arg-28. |
| HBGAA76R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 753 as residues: Ser-4 to Ser-11, Pro-27 to Asn-37. |
| HTXPI29R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 756 as residues: Thr-17 to Leu-24, Thr-57 to Tyr-67, Leu-92 to Phe-102, Asn-128 to Gln-134. |
| HBGAA54R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 760 as residues: Arg-62 to Leu-70, Ile-74 to Arg-79. |
| HDPJR77R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 763 as residues: Glu-7 to Lys-22, Thr-33 to Glu-39, Lys-69 to Glu-76, Asp-84 to Tyr-90. |
| HTTIO41R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 764 as residues: Val-17 to Ser-22, Arg-41 to Glu-46, Lys-50 to Pro-75, Ser-92 to Pro-100. |
| HDPUL86R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 767 as residues: Lys-7 to Gly-13. |
| HTXNT16R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 768 as residues: Leu-67 to Asn-72, Thr-102 to Phe-111, Gly-127 to Gln-135. |
| HLXNA54R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 770 as residues: Gln-1 to Glu-6, Pro-23 to Trp-31, Arg-46 to Trp-51. |
| H2LAX93R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 772 as residues: Glu-3 to Gln-10. |
| HWAFW10R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 773 as residues: Glu-13 to Asp-22, His-34 to Trp-40, Arg-69 to Lys-75. |
| HBGDD17R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 775 as residues: Arg-23 to Thr-28, Pro-40 to Glu-51, Ala-62 to His-68. |
| H2CBB43R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 778 as residues: Asp-90 to Asp-95, Arg-106 to Thr-117. |
| H2CBQ77R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 779 as residues: Asp-11 to Glu-16, Gln-19 to Tyr-24, Pro-34 to Gly-46. |
| HOEMK06R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 781 as residues: Pro-1 to Gln-14. |
| HCHAG30R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 783 as residues: Gly-1 to Trp-7. |
| HAEAI26R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 788 as residues: Lys-32 to Val-40, Arg-43 to Pro-51. |
| H2CBN76R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 791 as residues: Ala-17 to Leu-22, Thr-72 to Lys-77. |
| HAGFX49R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 792 as residues: Ala-10 to Leu-15, His-64 to Cys-71. |
| HTXKR32R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 794 as residues: Ser-2 to Gly-12, Glu-57 to Val-65. |
| H6EAF46R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 796 as residues: Arg-11 to Ser-21. |
| H2LAK40R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 798 as residues: Glu-11 to Lys-20, Pro-22 to Arg-28. |
| H2LAY71R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 799 as residues: Arg-26 to Leu-36, Gln-82 to Asp-101, Arg-103 to Arg-108, Arg-113 to Arg-131. |
| HASAW80R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 803 as |

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| | residues: Gly-1 to Arg-6, Ala-19 to Pro-27, Gly-34 to Phe-40. |
| HCHAF25R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 804 as residues: Ser-30 to Thr-40, Leu-78 to Val-85, Asp-92 to Ala-97. |
| HLTHH84R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 805 as residues: Glu-2 to Ala-8. |
| HADDC09R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 808 as residues: Leu-3 to Gly-9, Thr-20 to Gly-29. |
| HAQA110R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 811 as residues: Gly-1 to Lys-21. |
| HBGBT78R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 814 as residues: Asn-1 to Lys-22. |
| HBGCB06R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 815 as residues: Phe-1 to Phe-15. |
| HCHMW05R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 823 as residues: Pro-6 to Ser-11. |
| HODFW25R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 829 as residues: Ser-1 to Thr-8, Glu-17 to Ala-32, Arg-39 to Trp-47. |
| HOEMQ91R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 830 as residues: Arg-8 to Ser-13. |
| HOGBG56R | Preferred epitopes include those comprising a sequence shown in SEQ ID NO. 831 as residues: Lys-20 to Arg-25. |

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide sequence shown in SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by the cDNA in the related cDNA clone contained in a deposited library or encoded by a polynucleotide that hybridizes to the complement of an epitope encoding sequence of SEQ ID NO:X, or an epitope encoding sequence contained in the deposited cDNA clone under stringent hybridization conditions, or alternatively, under lower stringency hybridization conditions, as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to this complementary strand under stringent hybridization conditions or alternatively, under lower stringency hybridization conditions, as defined supra.

The term "epitopes," as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An "immunogenic epitope," as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998-4002 (1983)). The term "antigenic epitope," as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross-reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, R. A., Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985) further described in U.S. Patent No. 4,631,211.)

In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at

least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies, that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 10 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985)). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice

are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100 µg of peptide or carrier protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention, and immunogenic and/or antigenic epitope fragments thereof can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995).

Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, may be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for

immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); K. Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).)

5 Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et
10 al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., *Cell* 37:767 (1984).)

15 Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

20 Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed
25 in human cell lines (Janknecht et al., *Proc. Natl. Acad. Sci. USA* 88:8972- 897 (1991)). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto
30 Ni²⁺ nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

 Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities
30 of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al.,

Curr. Opinion Biotechnol. 8:724-33 (1997); Harayama, Trends Biotechnol. 16(2):76-82 (1998); Hansson, et al., J. Mol. Biol. 287:265-76 (1999); and Lorenzo and Blasco, Biotechniques 24(2):308- 13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides
5 corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-
10 prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

15 As discussed herein, any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on
20 trafficking signals, polypeptides of the present invention which are shown to be secreted can be used as targeting molecules once fused to other proteins.

Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker
25 sequences.

In certain preferred embodiments, proteins of the invention comprise fusion proteins wherein the polypeptides are N and/or C- terminal deletion mutants. In preferred embodiments, the application is directed to nucleic acid molecules at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to the nucleic acid sequences encoding polypeptides
30 having the amino acid sequence of the specific N- and C-terminal deletions mutants. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent
5 handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

10 Vectors, Host Cells, and Protein Production

The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral
15 vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

The polynucleotides of the invention may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then
20 transduced into host cells.

The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the E. coli lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable
25 promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

As indicated, the expression vectors will preferably include at least one selectable
30 marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in E. coli and other bacteria. Representative examples of appropriate hosts include,

but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells.

5 Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-10 3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, 15 pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.

Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in 20 many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid 25 extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

Polypeptides of the present invention can also be recovered from: products purified 30 from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast,

higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

In one embodiment, the yeast *Pichia pastoris* is used to express polypeptides of the invention in a eukaryotic system. *Pichia pastoris* is a methylotrophic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O_2 . This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O_2 . Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., et al., *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., et al., *Yeast* 5:167-77 (1989); Tschopp, J.F., et al., *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a polypeptide of the invention by virtue of the strong *AOX1* promoter linked to

the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYDI, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., Nature, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the

polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid, α -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, γ -Abu, ϵ -Ahx, 6-amino hexanoic acid, Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, β -alanine, fluoro-amino acids, designer amino acids such as β -methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

Non-naturally occurring variants may be produced using art-known mutagenesis techniques, which include, but are not limited to oligonucleotide mediated mutagenesis, alanine scanning, PCR mutagenesis, site directed mutagenesis (*see, e.g., Carter et al., Nucl. Acids Res. 13:4331 (1986); and Zoller et al., Nucl. Acids Res. 10:6487 (1982)*), cassette mutagenesis (*see, e.g., Wells et al., Gene 34:315 (1985)*), restriction selection mutagenesis (*see, e.g., Wells et al., Philos. Trans. R. Soc. London SerA 317:415 (1986)*).

The invention additionally, encompasses polypeptides of the present invention which are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH_4 ; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

Additional post-translational modifications encompassed by the invention include, for example, e.g., N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased

solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent No. 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog). For example, the polyethylene glycol may have an average molecular weight of about 200; 500; 1000; 1500; 2000; 2500; 3000; 3500; 4000; 4500; 5000; 5500; 6000; 6500; 7000; 7500; 8000; 8500; 9000; 9500; 10,000; 10,500; 11,000; 11,500; 12,000; 12,500; 13,000; 13,500; 14,000; 14,500; 15,000; 15,500; 16,000; 16,500; 17,000; 17,500; 18,000; 18,500; 19,000; 19,500; 20,000; 25,000; 30,000; 35,000; 40,000; 50,000; 55,000; 60,000; 65,000; 70,000; 75,000; 80,000; 85,000; 90,000; 95,000; or 100,000 kDa.

As noted above, the polyethylene glycol may have a branched structure. Branched polyethylene glycols are described, for example, in U.S. Patent No. 5,643,575; Morpurgo *et al.*, *Appl. Biochem. Biotechnol.* 56:59-72 (1996); Vorobjev *et al.*, *Nucleosides Nucleotides* 18:2745-2750 (1999); and Caliceti *et al.*, *Bioconjug. Chem.* 10:638-646 (1999), the disclosures of each of which are incorporated herein by reference.

The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik *et al.*, *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a

reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

As suggested above, polyethylene glycol may be attached to proteins via linkage to any of a number of amino acid residues. For example, polyethylene glycol can be linked to a proteins via covalent bonds to lysine, histidine, aspartic acid, glutamic acid, or cysteine residues. One or more reaction chemistries may be employed to attach polyethylene glycol to specific amino acid residues (e.g., lysine, histidine, aspartic acid, glutamic acid, or cysteine) of the protein or to more than one type of amino acid residue (e.g., lysine, histidine, aspartic acid, glutamic acid, cysteine and combinations thereof) of the protein.

One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

As indicated above, pegylation of the proteins of the invention may be accomplished by any number of means. For example, polyethylene glycol may be attached to the protein either directly or by an intervening linker. Linkerless systems for attaching polyethylene glycol to proteins are described in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-

304 (1992); Francis *et al.*, *Intern. J. of Hematol.* 68:1-18 (1998); U.S. Patent No. 4,002,531; U.S. Patent No. 5,349,052; WO 95/06058; and WO 98/32466, the disclosures of each of which are incorporated herein by reference.

One system for attaching polyethylene glycol directly to amino acid residues of proteins without an intervening linker employs tresylated MPEG, which is produced by the modification of monmethoxy polyethylene glycol (MPEG) using tresylchloride ($\text{ClSO}_2\text{CH}_2\text{CF}_3$). Upon reaction of protein with tresylated MPEG, polyethylene glycol is directly attached to amine groups of the protein. Thus, the invention includes protein-polyethylene glycol conjugates produced by reacting proteins of the invention with a polyethylene glycol molecule having a 2,2,2-trifluoroethane sulphonyl group.

Polyethylene glycol can also be attached to proteins using a number of different intervening linkers. For example, U.S. Patent No. 5,612,460, the entire disclosure of which is incorporated herein by reference, discloses urethane linkers for connecting polyethylene glycol to proteins. Protein-polyethylene glycol conjugates wherein the polyethylene glycol is attached to the protein by a linker can also be produced by reaction of proteins with compounds such as MPEG-succinimidylsuccinate, MPEG activated with 1,1'-carbonyldiimidazole, MPEG-2,4,5-trichloropenylcarbonate, MPEG-p-nitrophenolcarbonate, and various MPEG-succinate derivatives. A number additional polyethylene glycol derivatives and reaction chemistries for attaching polyethylene glycol to proteins are described in WO 98/32466, the entire disclosure of which is incorporated herein by reference. Pegylated protein products produced using the reaction chemistries set out herein are included within the scope of the invention.

The number of polyethylene glycol moieties attached to each protein of the invention (*i.e.*, the degree of substitution) may also vary. For example, the pegylated proteins of the invention may be linked, on average, to 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 17, 20, or more polyethylene glycol molecules. Similarly, the average degree of substitution within ranges such as 1-3, 2-4, 3-5, 4-6, 5-7, 6-8, 7-9, 8-10, 9-11, 10-12, 11-13, 12-14, 13-15, 14-16, 15-17, 16-18, 17-19, or 18-20 polyethylene glycol moieties per protein molecule. Methods for determining the degree of substitution are discussed, for example, in Delgado *et al.*, *Crit. Rev. Thera. Drug Carrier Sys.* 9:249-304 (1992).

The breast/ovarian cancer antigen polypeptides of the invention may be in monomers or multimers (*i.e.*, dimers, trimers, tetramers and higher multimers). Accordingly, the present

invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, Therapeutics) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or an amino acid sequence encoded by SEQ ID NO:X, and/or an amino acid sequence encoded by the cDNA in a related cDNA clone contained in a deposited library (including fragments, variants, splice variants, and fusion proteins, corresponding to any one of these as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (e.g., containing polypeptides having identical or different amino acid sequences) or a homotrimer (e.g., containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (i.e., polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention

contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:Y, or contained in a polypeptide encoded by SEQ ID NO:X, and/or by the cDNA in the related cDNA clone contained in a deposited library). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, osteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the

invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C-terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide

components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Antibodies

Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment, or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG,

IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')₂, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, sheep rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, or by size in contiguous amino acid residues. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that

specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention.

In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, or 10^{-15} M.

The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol.*

Chem. 272(17):11295-11301 (1997); Taryman et al., Neuron 14(4):755-762 (1995); Muller et al., Structure 6(9):1153-1167 (1998); Bartunek et al., Cytokine 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

Antibodies of the present invention may be used, for example, but not limited to, to
5 purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., Antibodies: A Laboratory Manual, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference
10 herein in its entirety).

As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other
15 compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

The antibodies of the invention include derivatives that are modified, i.e., by the
20 covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other
25 protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

The antibodies of the present invention may be generated by any suitable method
30 known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to

induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term "monoclonal antibody" as used herein is not limited to antibodies produced through hybridoma technology. The term "monoclonal antibody" refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by

fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')₂ fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')₂ fragments). F(ab')₂ fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any

desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')₂ fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entirety).

Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol. Methods* 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., *Nature* 332:323 (1988), which are incorporated herein by reference in their entirety.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein*

Engineering 7(6):805-814 (1994); Roguska. et al., PNAS 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, Int. Rev. Immunol. 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent

No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed
5 against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., Bio/technology 12:899-903
10 (1988)).

Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, FASEB J. 7(5):437-444; (1989) and Nissinoff, J. Immunol. 147(8):2429-2438 (1991)). For example, antibodies
15 which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For
20 example, such anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

Polynucleotides Encoding Antibodies

The invention further provides polynucleotides comprising a nucleotide sequence
25 encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or alternatively, under lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

30 The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be

assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., *BioTechniques* 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A+ RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR may then be cloned into replicable cloning vectors using any method well known in the art.

Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework

regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., J. Mol. Biol. 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

Methods of Producing Antibodies

The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein.

Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not

limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell
5 systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring
10 recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant
15 antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

In bacterial systems, a number of expression vectors may be advantageously selected
20 depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al.,
25 *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase
30 (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or

factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells.

- 5 The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

- In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence
10 of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan &
15 Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can
20 be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

- In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion
25 desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein. Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end,
30 eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERY, BHK, Hela, COS,

MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp^rt- or ap^rt- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci. USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215; and hyg^r, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.),

Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by
5 reference herein in their entireties.

The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing
10 antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

The host cell may be co-transfected with two expression vectors of the invention, the
15 first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to
20 avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci. USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method
25 known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide
30 sequences described herein or otherwise known in the art, to facilitate purification.

The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or

portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20,
5 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro
10 immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

The present invention further includes compositions comprising the polypeptides of
15 the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The
20 polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the
25 art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341(1992) (said references incorporated by reference in their entireties).

30 As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using

methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988)). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., J. Molecular Recognition 8:52-58 (1995); Johanson et al., J. Biol. Chem. 270:9459-9471 (1995)).

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., Cell 37:767 (1984)) and the "flag" tag.

The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent

materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include ^{125}I , ^{131}I , ^{111}In or ^{99}Tc .

Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytotoxic agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis- dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical

chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor, α -interferon, β -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic agent, e.g., TNF- α , TNF- β , AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

5 *Immunophenotyping*

The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types.

- 10 Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

- 15 These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

Assays For Antibody Binding

- 25 The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel *et al*, eds, 30 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York,

which is incorporated by reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X- 100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasylol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%- 20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., ³²P or ¹²⁵I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., 3H or 125I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., 3H or 125I) in the presence of increasing amounts of an unlabeled second antibody.

25 *Therapeutic Uses*

The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of

the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities

include those with a dissociation constant or K_d less than 5×10^{-2} M, 10^{-2} M, 5×10^{-3} M, 10^{-3} M, 5×10^{-4} M, 10^{-4} M, 5×10^{-5} M, 10^{-5} M, 5×10^{-6} M, 10^{-6} M, 5×10^{-7} M, 10^{-7} M, 5×10^{-8} M, 10^{-8} M, 5×10^{-9} M, 10^{-9} M, 5×10^{-10} M, 10^{-10} M, 5×10^{-11} M, 10^{-11} M, 5×10^{-12} M, 10^{-12} M, 5×10^{-13} M, 10^{-13} M, 5×10^{-14} M, 10^{-14} M, 5×10^{-15} M, and 10^{-15} M.

5

Gene Therapy

In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., *Clinical Pharmacy* 12:488-505 (1993); Wu and Wu, *Biotherapy* 3:87-95 (1991); Tolstoshev, *Ann. Rev. Pharmacol. Toxicol.* 32:573-596 (1993); Mulligan, *Science* 260:926-932 (1993); and Morgan and Anderson, *Ann. Rev. Biochem.* 62:191-217 (1993); May, *TIBTECH* 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), *Current Protocols in Molecular Biology*, John Wiley & Sons, NY (1993); and Kriegler, *Gene Transfer and Expression, A Laboratory Manual*, Stockton Press, NY (1990).

In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue-specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989)).

In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

5 Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

10 In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of
15 microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)) (which can be used to target
20 cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted in vivo for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be
25 introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989)).

30 In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., Meth. Enzymol. 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the

host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method

known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, *Cell* 71:973-985 (1992); Rheinwald, *Meth. Cell Bio.* 21A:229 (1980); and Pittelkow and Scott, *Mayo Clinic Proc.* 61:771 (1986)).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that

expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

15 *Therapeutic/Prophylactic Administration and Composition*

The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably a polypeptide or antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)), construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral

routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., *Macromol. Sci. Rev. Macromol. Chem.* 23:61 (1983); see also Levy et al., *Science* 228:190 (1985); During et al., *Ann. Neurol.* 25:351 (1989); Howard et al.,

J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

5 Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see 10 U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox- like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 15 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means 20 approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic 25 origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, 30 glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form

of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend

on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

5 For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the
10 foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

The invention also provides a pharmaceutical pack or kit comprising one or more
15 containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

20

Diagnosis and Imaging

Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity
25 of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide
30 gene expression level compared to the standard expression level is indicative of aberrant expression.

The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{125}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium (^{112}In), and technetium (^{99}Tc); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the

amount of labeled molecule detected to a standard value previously determined for a particular system.

It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of ^{99m}Tc. The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patent using positron emission-tomography. In yet another embodiment, the molecule

is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

Kits

5 The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present
10 invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes
15 the first antibody may be conjugated to a detectable substrate).

 In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated
20 polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically
25 synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

 In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of
30 the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

Uses of the Polynucleotides

Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

The breast/ovarian cancer antigen polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each sequence is specifically targeted to and can hybridize with a particular location on an individual human chromosome, thus each polynucleotide of the present invention can routinely be used as a chromosome marker using techniques known in the art.

Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably at least 15 bp (e.g., 15-25 bp) from the sequences shown in SEQ ID NO:X, or the complement thereto. Primers can optionally be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to SEQ ID NO:X will yield an amplified fragment.

Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled flow-sorted chromosomes, preselection by hybridization to construct chromosome specific-cDNA libraries, and computer mapping techniques (See, e.g., Shuler, Trends Biotechnol 16:456-459 (1998) which is hereby incorporated by reference in its entirety).

Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes).

Thus, the present invention also provides a method for chromosomal localization which involves (a) preparing PCR primers from the polynucleotide sequences in Table 3 and SEQ ID NO:X and (b) screening somatic cell hybrids containing individual chromosomes.

5 The polynucleotides of the present invention would likewise be useful for radiation hybrid mapping, HAPPY mapping, and long range restriction mapping. For a review of these techniques and others known in the art, see, e.g. Dear, "Genome Mapping: A Practical Approach," IRL Press at Oxford University Press, London (1997); Aydin, J. Mol. Med. 77:691-694 (1999); Hacia et al., Mol. Psychiatry 3:483-492 (1998); Herrick et al., Chromosome Res. 7:409-423 (1999); Hamilton et al., Methods Cell Biol. 62:265-280 (2000);
10 and/or Ott, J. Hered. 90:68-70 (1999) each of which is hereby incorporated by reference in its entirety.

Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular
15 disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library).) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

20 Thus, once coinheritance is established, differences in a polynucleotide of the invention and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all
25 affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

30 Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using the polynucleotides of the

invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention provides a method of detecting increased or decreased expression levels of the breast, ovarian, breast cancer and/or ovarian cancer polynucleotides in affected individuals as compared to unaffected individuals using polynucleotides of the present invention and techniques known in the art, including but not limited to the method described in Example 11. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer, involving measuring the expression level of breast/ovarian cancer antigen polynucleotides in breast and/or ovarian tissue or other cells or body fluid from an individual and comparing the measured gene expression level with a standard breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including breast cancer and/or ovarian cancer.

In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the invention, where each probe has one strand containing a 31'-mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

Where a diagnosis of a disorder related to the female reproductive system, particularly a disorder related to the breast and/or ovary, including, for example, diagnosis of a tumor, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed breast, ovarian, breast cancer and/or ovarian cancer polynucleotide expression will experience a

worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

By "measuring the expression level of breast, ovarian, breast cancer and/or ovarian cancer polynucleotides" is intended qualitatively or quantitatively measuring or estimating
5 the level of the breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the level of the mRNA encoding the breast, ovarian, breast cancer and/or ovarian cancer polypeptide in a first biological sample either directly (e.g., by determining or estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in a second biological sample).
10 Preferably, the breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the female reproductive system related disorder or being determined by averaging
15 levels from a population of individuals not having a female reproductive system related disorder. As will be appreciated in the art, once a standard breast, ovarian, breast cancer and/or ovarian cancer polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

By "biological sample" is intended any biological sample obtained from an
20 individual, body fluid, cell line, tissue culture, or other source which contains breast, ovarian, breast cancer and/or ovarian cancer polypeptide or the corresponding mRNA. As indicated, biological samples include body fluids (such as vaginal pool, breast milk, lymph, sera, plasma, urine, semen, synovial fluid and spinal fluid) which contain the breast, ovarian, breast cancer and/or ovarian cancer polypeptide, breast and/or ovarian tissue, and other tissue
25 sources found to express the breast, ovarian, breast cancer and/or ovarian cancer polypeptide. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides of the invention are attached to a
30 solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with breast, ovarian, breast cancer and/or ovarian cancer polynucleotides attached may

be used to identify polymorphisms between the breast, ovarian, breast cancer and/or ovarian cancer polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, such as for example, in neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, though most preferably in breast and/or ovarian related proliferative, and/or cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

The present invention encompasses breast, ovarian, breast cancer and/or ovarian cancer polynucleotides that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides of the invention are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, *Science* 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, *Nature* 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point (T_{sub.m}) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

The present invention have uses which include, but are not limited to, detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

Pathological cell proliferative disorders are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in Neoplastic Diseases of the Blood, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580).

However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., Proc. Natl. Acad. Sci. 85:1028 (1988); Anfossi et al., Proc. Natl. Acad. Sci. 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness is not limited to treatment of proliferative disorders of hematopoietic

cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

In addition to the foregoing, a breast/ovarian cancer antigen polynucleotide can be used to control gene expression through triple helix formation or through antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. *Neurochem.* 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al., *Nucleic Acids Research* 6: 3073 (1979); Cooney et al., *Science* 241: 456 (1988); and Dervan et al., *Science* 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., *Nucl. Acids Res.* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1360 (1991)) or to the mRNA itself (antisense - Okano, J. *Neurochem.* 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. The oligonucleotide described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of polypeptide of the present invention antigens. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat disease, and in particular, for the treatment of proliferative diseases and/or conditions.

Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed

on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

5 The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA
10 sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues,
15 e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erich, H., PCR Technology, Freeman and Co. (1992).) Once these specific
20 polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

There is also a need for reagents capable of identifying the source of a particular
25 tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to breast, ovarian, breast cancer and/or ovarian cancer polynucleotides prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue
30 cultures for contamination.

The polynucleotides of the present invention are also useful as hybridization probes for differential identification of the tissue(s) or cell type(s) present in a biological sample.

Similarly, polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays) or cell type(s) (e.g., immunocytochemistry assays). In addition, for a number of disorders of the above tissues or cells, significantly higher or lower
5 levels of gene expression of the polynucleotides/polypeptides of the present invention may be detected in certain tissues (e.g., tissues expressing polypeptides and/or polynucleotides of the present invention, breast, ovarian, breast cancer and/or ovarian cancer tissues and/or cancerous and/or wounded tissues) or bodily fluids (e.g., vaginal pool, breast milk, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder,
10 relative to a "standard" gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

Thus, the invention provides a diagnostic method of a disorder, which involves: (a) assaying gene expression level in cells or body fluid of an individual; (b) comparing the gene expression level with a standard gene expression level, whereby an increase or decrease in
15 the assayed gene expression level compared to the standard expression level is indicative of a disorder.

In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the
20 process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

Uses of the Polypeptides

25 Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

Polypeptides and antibodies directed to polypeptides of the present invention are useful to provide immunological probes for differential identification of the tissue(s) (e.g., immunohistochemistry assays such as, for example, ABC immunoperoxidase (Hsu et al., J.
30 Histochem. Cytochem. 29:577-580 (1981)) or cell type(s) (e.g., immunocytochemistry assays).

Antibodies can be used to assay levels of polypeptides encoded by polynucleotides of the invention in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell. Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for

5 detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium

10 (^{68}Ga , ^{67}Ga), palladium (^{103}Pd), molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F), ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru ; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

In addition to assaying levels of polypeptide of the present invention in a biological

15 sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be

20 incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example, ^{131}I , ^{112}In , $^{99\text{m}}\text{Tc}$, (^{131}I , ^{125}I , ^{123}I , ^{121}I), carbon (^{14}C), sulfur (^{35}S), tritium (^3H), indium ($^{115\text{m}}\text{In}$, $^{113\text{m}}\text{In}$, ^{112}In , ^{111}In), and technetium (^{99}Tc , $^{99\text{m}}\text{Tc}$), thallium (^{201}Tl), gallium (^{68}Ga , ^{67}Ga), palladium (^{103}Pd),

25 molybdenum (^{99}Mo), xenon (^{133}Xe), fluorine (^{18}F , ^{153}Sm , ^{177}Lu , ^{159}Gd , ^{149}Pm , ^{140}La , ^{175}Yb , ^{166}Ho , ^{90}Y , ^{47}Sc , ^{186}Re , ^{188}Re , ^{142}Pr , ^{105}Rh , ^{97}Ru), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously or intraperitoneally) into the mammal to be examined for immune system disorder. It will be understood in the art that the size of the subject and the imaging system

30 used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of $^{99\text{m}}\text{Tc}$. The labeled antibody or

antibody fragment will then preferentially accumulate at the location of cells which express the polypeptide encoded by a polynucleotide of the invention. *In vivo* tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments" (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982)).

In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (e.g., polypeptides encoded by polynucleotides of the invention and/or antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention in association with toxins or cytotoxic prodrugs.

By "toxin" is meant one or more compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. "Toxin" also includes a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example, ^{213}Bi , or other radioisotopes such as, for example, ^{103}Pd , ^{133}Xe , ^{131}I , ^{68}Ge , ^{57}Co , ^{65}Zn , ^{85}Sr , ^{32}P , ^{35}S , ^{90}Y , ^{153}Sm , ^{153}Gd , ^{169}Yb , ^{51}Cr , ^{54}Mn , ^{75}Se , ^{113}Sn , $^{90}\text{Yttrium}$, ^{117}Tin , $^{186}\text{Rhenium}$, $^{166}\text{Holmium}$, and $^{188}\text{Rhenium}$; luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

Techniques known in the art may be applied to label polypeptides of the invention (including antibodies). Such techniques include, but are not limited to, the use of bifunctional conjugating agents (see e.g., U.S. Patent Nos. 5,756,065; 5,714,631; 5,696,239; 5,652,361; 5,505,931; 5,489,425; 5,435,990; 5,428,139; 5,342,604; 5,274,119; 4,994,560; and 5,808,003; the contents of each of which are hereby incorporated by reference in its entirety).

Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer polypeptide of the present invention in cells or body fluid of an individual, or more preferably, assaying the expression level of a breast, ovarian, breast cancer and/or ovarian cancer of the present invention in breast and/or ovarian cells or vaginal pool or breast milk of an individual; and (b) comparing the assayed polypeptide expression level with a standard polypeptide expression level, whereby an increase or decrease in the assayed polypeptide expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Moreover, breast/ovarian cancer antigen polypeptides of the present invention can be used to treat or prevent diseases or conditions such as, for example, neural disorders, immune system disorders, muscular disorders, reproductive disorders, gastrointestinal disorders, pulmonary disorders, cardiovascular disorders, renal disorders, proliferative disorders, and/or cancerous diseases and conditions, preferably proliferative disorders of the breast and/or ovary, and/or cancerous disease and conditions. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing

inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat disease (as described supra, and elsewhere herein). For example, administration of an antibody directed to a polypeptide of the present invention can bind, and/or neutralize the polypeptide, and/or reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

Gene Therapy Methods

Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of the polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the present invention operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the present invention ex vivo, with the engineered cells then being provided to a patient to be treated with the polypeptide of the present invention. Such methods are well-known in the art. For example, see Belldgrun, A., et al., J. Natl. Cancer Inst. 85: 207-216 (1993); Ferrantini, M. et al., Cancer Research 53: 1107-1112 (1993); Ferrantini, M. et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura, H., et al., Cancer Research 50: 5102-5106 (1990); Santodonato, L., et al., Human Gene Therapy 7:1-10 (1996);

Santodonato, L., et al., *Gene Therapy* 4:1246-1255 (1997); and Zhang, J. F. et al., *Cancer Gene Therapy* 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

In one embodiment, the polynucleotide of the present invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotide of the present invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

Any strong promoter known to those skilled in the art can be used for driving the expression of the polynucleotide sequence. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoA1 promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-

actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotide of the present invention.

Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into
5 cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis,
10 ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the
15 lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example,
20 stem cells of blood or skin fibroblasts. In vivo muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked nucleic acid sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more
25 preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

30 The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues,

throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

In certain embodiments, the polynucleotide constructs are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA (1989) 86:6077-6081, which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem. (1990) 265:10189-10192, which is herein incorporated by reference), in functional form.

Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA (1987) 84:7413-7416, which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).

Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication No. WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., P. Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG),
5 dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can
10 be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat
15 Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

20 The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology* (1983), 101:512-527, which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by
25 depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate
30 solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to

the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include Ca^{2+} -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta* (1975) 394:483; Wilson et al., *Cell* (1979) 17:77); ether injection (Deamer, D. and Bangham, A., *Biochim. Biophys. Acta* (1976) 443:629; Ostro et al., *Biochem. Biophys. Res. Commun.* (1977) 76:836; Fraley et al., *Proc. Natl. Acad. Sci. USA* (1979) 76:3348); detergent dialysis (Enoch, H. and Strittmatter, P., *Proc. Natl. Acad. Sci. USA* (1979) 76:145); and reverse-phase evaporation (REV) (Fraley et al., *J. Biol. Chem.* (1980) 255:10431; Szoka, F. and Papahadjopoulos, D., *Proc. Natl. Acad. Sci. USA* (1978) 75:145; Schaefer-Ridder et al., *Science* (1982) 215:166), which are
10 herein incorporated by reference.

Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

U.S. Patent No. 5,676,954 (which is herein incorporated by reference) reports on the
15 injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no. WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication no.
20 WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

In certain embodiments, cells are engineered, ex vivo or in vivo, using a retroviral particle containing RNA which comprises a sequence encoding a polypeptide of the present invention. Retroviruses from which the retroviral plasmid vectors may be derived include,
25 but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are
30 not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, *Human Gene Therapy* 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector

may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO_4 precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

5 The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding a polypeptide of the present invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either in vitro or in vivo. The transduced eukaryotic cells will express a polypeptide of the present invention.

10 In certain other embodiments, cells are engineered, ex vivo or in vivo, with polynucleotide contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses a polypeptide of the present invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have
15 been used as live enteric vaccines for many years with an excellent safety profile (Schwartz, A. R. et al. (1974) Am. Rev. Respir. Dis. 109:233-238). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld, M. A. et al. (1991) Science 252:431-434; Rosenfeld et al., (1992) Cell 68:143-155). Furthermore, extensive
20 studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green, M. et al. (1979) Proc. Natl. Acad. Sci. USA 76:6606).

 Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel. 3:499-503 (1993); Rosenfeld et al., Cell 68:143-155 (1992); Engelhardt et al., Human Genet. Ther. 4:759-769 (1993); Yang et al.,
25 Nature Genet. 7:362-369 (1994); Wilson et al., Nature 365:691-692 (1993); and U.S. Patent No. 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to
30 Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

In certain other embodiments, the cells are engineered, ex vivo or in vivo, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, N., Curr. Topics in Microbiol. Immunol. 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct. These viral particles are then used to transduce eukaryotic cells, either ex vivo or in vivo. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express a polypeptide of the invention.

Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding a polypeptide of the present invention) via homologous recombination (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc.

Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

Preferably, the polynucleotide encoding a polypeptide of the present invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the

cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppository solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers (Kaneda et al., Science 243:375 (1989)).

A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries. Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA 189:11277-11281, 1992, which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such

carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.

Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian.

Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly preferred.

15 **Biological Activities**

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, can be used in assays to test for one or more biological activities. If these polynucleotides or polypeptides, or agonists or antagonists of the present invention, do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides and polypeptides, and agonists or antagonists could be used to treat the associated disease.

Immune Activity

A polypeptide or polynucleotide, or agonists or antagonists of the present invention may be useful in treating deficiencies or disorders of the immune system, by activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune deficiencies or disorders may be genetic, somatic, such as cancer or some autoimmune disorders, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides or polypeptides, or

agonists or antagonists of the present invention can be used as a marker or detector of a particular immune system disease or disorder.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may be useful in treating or detecting deficiencies or disorders of hematopoietic cells.

5 Polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat those disorders associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein disorders (e.g. 10 agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

15 Moreover, polynucleotides or polypeptides, or agonists or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, or agonists or antagonists of the present invention could be used to treat blood coagulation disorders (e.g., afibrinogenemia, 20 factor deficiencies), blood platelet disorders (e.g. thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides or polypeptides, or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment of heart attacks (infarction), strokes, or scarring.

25 Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be useful in treating or detecting autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides or polypeptides, or agonists or 30 antagonists of the present invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

Examples of autoimmune disorders that can be treated or detected include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitis, and autoimmune inflammatory eye disease.

Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Moreover, these molecules can be used to treat anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

Polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to treat and/or prevent organ rejection or graft-versus-host disease (GVHD). Organ rejection occurs by host immune cell destruction of the transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. The administration of polynucleotides or polypeptides, or agonists or antagonists of the present invention that inhibits an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

Similarly, polynucleotides or polypeptides, or agonists or antagonists of the present invention may also be used to modulate inflammation. For example, polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation and differentiation of cells involved in an inflammatory response. These molecules can be used to treat inflammatory conditions, both chronic and acute conditions, including chronic prostatitis, granulomatous prostatitis and malacoplakia, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, or resulting from over production of cytokines (e.g., TNF or IL-1.)

Hyperproliferative Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used to treat or detect hyperproliferative disorders, including neoplasms. Polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, Polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative disorders can be treated. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating hyperproliferative disorders, such as a chemotherapeutic agent.

Examples of hyperproliferative disorders that can be treated or detected by Polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention. Examples of such hyperproliferative disorders include, but are not limited to: hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

Thus, the present invention provides a method for treating cell proliferative disorders by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

Another embodiment of the present invention provides a method of treating cell-proliferative disorders in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e. to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes" is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403

(1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral
5 (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-
10 dividing normal cells.

The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The polynucleotides of the present invention may also be administered to disease sites at the time
15 of surgical intervention.

By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

20 Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells.

25 The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

30 The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating one or more of the described disorders. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal

antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

In particular, the antibodies, fragments and derivatives of the present invention are useful for treating a subject having or developing cell proliferative and/or differentiation disorders as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example., which serve to increase the number or activity of effector cells which interact with the antibodies.

It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or K_d less than $5 \times 10^{-6}M$, $10^{-6}M$, $5 \times 10^{-7}M$, $10^{-7}M$, $5 \times 10^{-8}M$, $10^{-8}M$, $5 \times 10^{-9}M$, $10^{-9}M$, $5 \times 10^{-10}M$, $10^{-10}M$, $5 \times 10^{-11}M$, $10^{-11}M$, $5 \times 10^{-12}M$, $10^{-12}M$, $5 \times 10^{-13}M$, $10^{-13}M$, $5 \times 10^{-14}M$, $10^{-14}M$, $5 \times 10^{-15}M$, and $10^{-15}M$.

Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998),

which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al., *Cancer Metastasis Rev.* 17(2):155-61 (1998), which is hereby incorporated by reference)).

5 Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1
10 and -2 (See Schulze-Osthoff K, et.al., *Eur J Biochem* 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the
15 expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, *Mutat Res* 400(1-2):447-55 (1998), *Med Hypotheses*.50(5):423-33 (1998), *Chem Biol Interact.* Apr 24;111-112:23-34 (1998), *J Mol Med.*76(6):402-12 (1998), *Int J Tissue React*;20(1):3-15 (1998), which are all hereby incorporated by reference).

20 Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., *Curr Top Microbiol Immunol* 1998;231:125-41, which is hereby incorporated by reference). Such
25 therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or
30 polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with with

heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

10 Cardiovascular Disorders

Polynucleotides or polypeptides, or agonists or antagonists of the present invention, may be used to treat cardiovascular disorders, including peripheral artery disease, such as limb ischemia.

Cardiovascular disorders include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilog of Fallot, ventricular heart septal defects.

Cardiovascular disorders also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

Heart valve disease include aortic valve insufficiency, aortic valve stenosis, heart murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomas, bacillary angiomas, Hippiel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema, aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, ataxia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

5 Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

Cerebrovascular disorders include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis,
10 carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

15 Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

20 Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

25 Polynucleotides or polypeptides, or agonists or antagonists of the present invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge
30 depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides may be administered as part of a

Therapeutic, described in more detail below. Methods of delivering polynucleotides are described in more detail herein.

Anti-Angiogenesis Activity

5 The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and
10 spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye
15 disorders, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995); Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological
20 conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

 The polynucleotides encoding a polypeptide of the present invention may be administered along with other polynucleotides encoding an angiogenic protein. Examples of
25 angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide
30 synthase.

 The present invention provides for treatment of diseases or disorders associated with neovascularization by administration of the polynucleotides and/or polypeptides of the

invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, Medicine, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat a cancer or tumor. Cancers which may be treated with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including breast, ovarian, prostate, lung, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating other disorders, besides cancers, which involve angiogenesis. These disorders include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid

arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque
5 neovascularization; telangiectasia; hemophiliac joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

For example, within one aspect of the present invention methods are provided for treating hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar
10 or keloid.

Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of
15 hypertrophic scars and keloids (e.g., burns), and is preferably initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental
20 fibroplasia and macular degeneration.

Moreover, Ocular disorders associated with neovascularization which can be treated with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular
25 degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalm.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalm.* 22:291-312 (1978).

Thus, within one aspect of the present invention methods are provided for treating
30 neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation

of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of disorders can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbal corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbal cornea interspersed between the corneal lesion and its undesired

potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

- 5 Within another aspect of the present invention, methods are provided for treating neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat early forms of neovascular glaucoma.
- 10 Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating proliferative diabetic retinopathy, comprising the step of administering to a patient a
- 15 therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

- Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist
- 20 in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

- Within another aspect of the present invention, methods are provided for treating retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such
- 25 that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

- Additionally, disorders which can be treated with the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic
- 30 joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

Moreover, disorders and/or states, which can be treated with the the polynucleotides, polypeptides, agonists and/or agonists include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochela minalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or agonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

Polynucleotides, polypeptides, agonists and/or agonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

Polynucleotides, polypeptides, agonists and/or agonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a compositions (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g., in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated

with anti-angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors. Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for
5 example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate,
10 sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide,
15 molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine
20 sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline,
25 alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradecasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium
30 Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-

chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxynaminolmidazole; and metalloproteinase inhibitors such as BB94.

5 **Diseases at the Cellular Level**

Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as antagonists or agonists of the present invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon
10 cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary
15 cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression,
20 and/or metasis of cancers, in particular those listed above.

Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute
25 lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not
30 limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's

tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

Diseases associated with increased apoptosis that could be treated or detected by polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestasis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

Wound Healing and Epithelial Cell Proliferation

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity

wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and
5 antimetabolites. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote dermal reestablishment subsequent to dermal loss

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to increase the adherence of skin grafts to a wound bed and to
10 stimulate re-epithelialization from the wound bed. The following are types of grafts that polynucleotides or polypeptides, agonists or antagonists of the present invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft, epidermic graft, fascia graft, full thickness
15 graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omenpal graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, can be used to promote skin strength and to improve the appearance of aged skin.

20 It is believed that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intesting, and large intestine. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes,
25 type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. Polynucleotides or polypeptides, agonists or antagonists of the present invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present
30 invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may have a cytoprotective effect on

the small intestine mucosa. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating reepithelialization of these lesions. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with polynucleotides or polypeptides, agonists or antagonists of the present invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat diseases associated with the under expression.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to prevent and heal damage to the lungs due to various pathological states. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated using polynucleotides or

polypeptides, agonists or antagonists of the present invention. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

In addition, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

Neurological Diseases

In accordance with yet a further aspect of the present invention, there is provided a process for utilizing polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, for therapeutic purposes, for example, to stimulate neurological cell proliferation and/or differentiation. Therefore, polynucleotides, polypeptides, agonists and/or antagonists of the invention may be used to treat and/or detect neurologic diseases. Moreover, polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used as a marker or detector of a particular nervous system disease or disorder.

Examples of neurologic diseases which can be treated or detected with polynucleotides, polypeptides, agonists, and/or antagonists of the present invention include brain diseases, such as metabolic brain diseases which includes phenylketonuria such as maternal phenylketonuria, pyruvate carboxylase deficiency, pyruvate dehydrogenase complex deficiency, Wernicke's Encephalopathy, brain edema, brain neoplasms such as

cerebellar neoplasms which include infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms, supratentorial neoplasms, canavan disease, cerebellar diseases such as cerebellar ataxia which include spinocerebellar degeneration such as ataxia telangiectasia, cerebellar dyssynergia, Friederich's Ataxia, Machado-Joseph Disease, olivopontocerebellar atrophy, cerebellar neoplasms such as infratentorial neoplasms, diffuse cerebral sclerosis such as encephalitis periaxialis, globoid cell leukodystrophy, metachromatic leukodystrophy and subacute sclerosing panencephalitis, cerebrovascular disorders (such as carotid artery diseases which include carotid artery thrombosis, carotid stenosis and Moyamoya Disease, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral embolism and thrombosis such as carotid artery thrombosis, sinus thrombosis and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as transient cerebral ischemia, Subclavian Steal Syndrome and vertebrobasilar insufficiency, vascular dementia such as multi-infarct dementia, periventricular leukomalacia, vascular headache such as cluster headache, migraine, dementia such as AIDS Dementia Complex, presenile dementia such as Alzheimer's Disease and Creutzfeldt-Jakob Syndrome, senile dementia such as Alzheimer's Disease and progressive supranuclear palsy, vascular dementia such as multi-infarct dementia, encephalitis which include encephalitis periaxialis, viral encephalitis such as epidemic encephalitis, Japanese Encephalitis, St. Louis Encephalitis, tick-borne encephalitis and West Nile Fever, acute disseminated encephalomyelitis, meningoencephalitis such as uveomeningoencephalitic syndrome, Postencephalitic Parkinson Disease and subacute sclerosing panencephalitis, encephalomalacia such as periventricular leukomalacia, epilepsy such as generalized epilepsy which includes infantile spasms, absence epilepsy, myoclonic epilepsy which includes MERRF Syndrome, tonic-clonic epilepsy, partial epilepsy such as complex partial epilepsy, frontal lobe epilepsy and temporal lobe epilepsy, post-traumatic epilepsy, status epilepticus such as Epilepsia Partialis Continua, Hallervorden-Spatz Syndrome, hydrocephalus such as Dandy-Walker Syndrome and normal pressure hydrocephalus, hypothalamic diseases such as hypothalamic neoplasms, cerebral malaria, narcolepsy which includes cataplexy, bulbar poliomyelitis, cerebri pseudotumor, Rett Syndrome, Reye's Syndrome, thalamic diseases, cerebral toxoplasmosis, intracranial tuberculoma and Zellweger Syndrome, central nervous

system infections such as AIDS Dementia Complex, Brain Abscess, subdural empyema, encephalomyelitis such as Equine Encephalomyelitis, Venezuelan Equine Encephalomyelitis, Necrotizing Hemorrhagic Encephalomyelitis, Visna, cerebral malaria, meningitis such as arachnoiditis, aseptic meningitis such as viral meningitis which includes lymphocytic choriomeningitis. Bacterial meningitis which includes Haemophilus Meningitis, Listeria Meningitis, Meningococcal Meningitis such as Waterhouse-Friderichsen Syndrome, Pneumococcal Meningitis and meningeal tuberculosis, fungal meningitis such as Cryptococcal Meningitis, subdural effusion, meningoencephalitis such as uvemeningoencephalitic syndrome, myelitis such as transverse myelitis, neurosyphilis such as tabes dorsalis, poliomyelitis which includes bulbar poliomyelitis and postpoliomyelitis syndrome, prion diseases (such as Creutzfeldt-Jakob Syndrome, Bovine Spongiform Encephalopathy, Gerstmann-Straussler Syndrome, Kuru, Scrapie) cerebral toxoplasmosis, central nervous system neoplasms such as brain neoplasms that include cerebellar neoplasms such as infratentorial neoplasms, cerebral ventricle neoplasms such as choroid plexus neoplasms, hypothalamic neoplasms and supratentorial neoplasms, meningeal neoplasms, spinal cord neoplasms which include epidural neoplasms, demyelinating diseases such as Canavan Diseases, diffuse cerebral sclerolysis which includes adrenoleukodystrophy, encephalitis periaxialis, globoid cell leukodystrophy, diffuse cerebral sclerosis such as metachromatic leukodystrophy, allergic encephalomyelitis, necrotizing hemorrhagic encephalomyelitis, progressive multifocal leukoencephalopathy, multiple sclerosis, central pontine myelinolysis, transverse myelitis, neuromyelitis optica, Scrapie, Swayback, Chronic Fatigue Syndrome, Visna, High Pressure Nervous Syndrome, Meningism, spinal cord diseases such as amyotonia congenita, amyotrophic lateral sclerosis, spinal muscular atrophy such as Werdnig-Hoffmann Disease, spinal cord compression, spinal cord neoplasms such as epidural neoplasms, syringomyelia, Tabes Dorsalis, Stiff-Man Syndrome, mental retardation such as Angelman Syndrome, Cri-du-Chat Syndrome, De Lange's Syndrome, Down Syndrome, Gangliosidoses such as gangliosidoses G(M1), Sandhoff Disease, Tay-Sachs Disease, Hartnup Disease, homocystinuria, Laurence-Moon- Biedl Syndrome, Lesch-Nyhan Syndrome, Maple Syrup Urine Disease, mucopolipidosis such as fucosidosis, neuronal ceroid-lipofuscinosis, oculocerebrorenal syndrome, phenylketonuria such as maternal phenylketonuria, Prader-Willi Syndrome, Rett Syndrome, Rubinstein-Taybi Syndrome, Tuberous Sclerosis, WAGR Syndrome, nervous system abnormalities such as

holoprosencephaly, neural tube defects such as anencephaly which includes hydrangencephaly, Arnold-Chairi Deformity, encephalocele, meningocele, meningomyelocele, spinal dysraphism such as spina bifida cystica and spina bifida occulta, hereditary motor and sensory neuropathies which include Charcot-Marie Disease, Hereditary
5 optic atrophy, Refsum's Disease, hereditary spastic paraplegia, Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies such as Congenital Analgesia and Familial Dysautonomia, Neurologic manifestations (such as agnosia that include Gerstmann's Syndrome, Amnesia such as retrograde amnesia, apraxia, neurogenic bladder, cataplexy, communicative disorders such as hearing disorders that includes deafness, partial hearing
10 loss, loudness recruitment and tinnitus, language disorders such as aphasia which include agraphia, anomia, broca aphasia, and Wernicke Aphasia, Dyslexia such as Acquired Dyslexia, language development disorders, speech disorders such as aphasia which includes anomia, broca aphasia and Wernicke Aphasia, articulation disorders, communicative disorders such as speech disorders which include dysarthria, echolalia, mutism and stuttering,
15 voice disorders such as aphonia and hoarseness, decerebrate state, delirium, fasciculation, hallucinations, meningism, movement disorders such as angelman syndrome, ataxia, athetosis, chorea, dystonia, hypokinesia, muscle hypotonia, myoclonus, tic, torticollis and tremor, muscle hypertonia such as muscle rigidity such as stiff-man syndrome, muscle spasticity, paralysis such as facial paralysis which includes Herpes Zoster Oticus,
20 Gastroparesis, Hemiplegia, ophthalmoplegia such as diplopia, Duane's Syndrome, Horner's Syndrome, Chronic progressive external ophthalmoplegia such as Kearns Syndrome, Bulbar Paralysis, Tropical Spastic Paraparesis, Paraplegia such as Brown-Sequard Syndrome, quadriplegia, respiratory paralysis and vocal cord paralysis, paresis, phantom limb, taste disorders such as ageusia and dysgeusia, vision disorders such as amblyopia, blindness, color
25 vision defects, diplopia, hemianopsia, scotoma and subnormal vision, sleep disorders such as hypersomnia which includes Kleine-Levin Syndrome, insomnia, and somnambulism, spasm such as trismus, unconsciousness such as coma, persistent vegetative state and syncope and vertigo, neuromuscular diseases such as amyotonia congenita, amyotrophic lateral sclerosis, Lambert-Eaton Myasthenic Syndrome, motor neuron disease, muscular atrophy such as
30 spinal muscular atrophy, Charcot-Marie Disease and Werdnig-Hoffmann Disease, Postpoliomyelitis Syndrome, Muscular Dystrophy, Myasthenia Gravis, Myotonia Atrophica, Myotonia Confenita, Nemaline Myopathy, Familial Periodic Paralysis, Multiplex

Paramyoclonus, Tropical Spastic Paraparesis and Stiff-Man Syndrome, peripheral nervous system diseases such as acrodynia, amyloid neuropathies, autonomic nervous system diseases such as Adie's Syndrome, Barre-Lieou Syndrome, Familial Dysautonomia, Horner's Syndrome, Reflex Sympathetic Dystrophy and Shy-Drager Syndrome, Cranial Nerve Diseases such as Acoustic Nerve Diseases such as Acoustic Neuroma which includes Neurofibromatosis 2, Facial Nerve Diseases such as Facial Neuralgia, Melkersson-Rosenthal Syndrome, ocular motility disorders which includes amblyopia, nystagmus, oculomotor nerve paralysis, ophthalmoplegia such as Duane's Syndrome, Horner's Syndrome, Chronic Progressive External Ophthalmoplegia which includes Kearns Syndrome, Strabismus such as Esotropia and Exotropia, Oculomotor Nerve Paralysis, Optic Nerve Diseases such as Optic Atrophy which includes Hereditary Optic Atrophy, Optic Disk Drusen, Optic Neuritis such as Neuromyelitis Optica, Papilledema, Trigeminal Neuralgia, Vocal Cord Paralysis, Demyelinating Diseases such as Neuromyelitis Optica and Swayback, Diabetic neuropathies such as diabetic foot, nerve compression syndromes such as carpal tunnel syndrome, tarsal tunnel syndrome, thoracic outlet syndrome such as cervical rib syndrome, ulnar nerve compression syndrome, neuralgia such as causalgia, cervico-brachial neuralgia, facial neuralgia and trigeminal neuralgia, neuritis such as experimental allergic neuritis, optic neuritis, polyneuritis, polyradiculoneuritis and radiculities such as polyradiculitis, hereditary motor and sensory neuropathies such as Charcot-Marie Disease, Hereditary Optic Atrophy, Refsum's Disease, Hereditary Spastic Paraplegia and Werdnig-Hoffmann Disease, Hereditary Sensory and Autonomic Neuropathies which include Congenital Analgesia and Familial Dysautonomia, POEMS Syndrome, Sciatica, Gustatory Sweating and Tetany).

Infectious Disease

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to treat or detect infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papiloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a variety of diseases or symptoms, including, but not limited to: arthritis, bronchiolitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat AIDS.

Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated or detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia

(e.g., *Borrelia burgdorferi*, Brucellosis, Candidiasis, *Campylobacter*, *Coccidioidomycosis*, *Cryptococcosis*, *Dermatocycoses*, *E. coli* (e.g., Enterotoxigenic *E. coli* and Enterohemorrhagic *E. coli*), *Enterobacteriaceae* (*Klebsiella*, *Salmonella* (e.g., *Salmonella typhi*, and *Salmonella paratyphi*), *Serratia*, *Yersinia*), *Erysipelothrix*, *Helicobacter*,
5 *Legionellosis*, *Leptospirosis*, *Listeria*, *Mycoplasmatales*, *Mycobacterium leprae*, *Vibrio cholerae*, *Neisseriaceae* (e.g., *Acinetobacter*, *Gonorrhea*, *Menigococcal*), *Meisseria meningitidis*, *Pasteurellacea* Infections (e.g., *Actinobacillus*, *Heamophilus* (e.g., *Heamophilus influenza type B*), *Pasteurella*), *Pseudomonas*, *Rickettsiaceae*, *Chlamydiaceae*, *Syphilis*, *Shigella* spp., *Staphylococcal*, *Meningiococcal*, *Pneumococcal* and *Streptococcal* (e.g.,
10 *Streptococcus pneumoniae* and Group B *Streptococcus*). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme
15 Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, *Gonorrhea*, meningitis (e.g., meningitis types A and B), *Chlamydia*, *Syphilis*, *Diphtheria*, *Leprosy*, *Paratuberculosis*, *Tuberculosis*, *Lupus*, *Botulism*, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections.
20 Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases. In specific embodiments, Ppolynucleotides, polypeptides, agonists or antagonists of the invention are used to treat: tetanus, *Diphtheria*, botulism, and/or meningitis type B.

Moreover, parasitic agents causing disease or symptoms that can be treated or
25 detected by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, *Cryptosporidiosis*, *Dientamoebiasis*, *Dourine*, *Ectoparasitic*, *Giardiasis*, *Helminthiasis*, *Leishmaniasis*, *Theileriasis*, *Toxoplasmosis*, *Trypanosomiasis*, and *Trichomonas* and *Sporozoans* (e.g., *Plasmodium virax*, *Plasmodium falciparum*,
30 *Plasmodium malariae* and *Plasmodium ovale*). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic

infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat or detect any of these symptoms or diseases.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (ex vivo therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

Regeneration

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

Moreover, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage. Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

Similarly, nerve and brain tissue could also be regenerated by using polynucleotides or polypeptides, as well as agonists or antagonists of the present invention, to proliferate and differentiate nerve cells. Diseases that could be treated using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic disorders (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated using the polynucleotides or polypeptides, as well as agonists or antagonists of the present invention.

Chemotaxis

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

Polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat inflammation, infection, hyperproliferative disorders, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat wounds.

It is also contemplated that polynucleotides or polypeptides, as well as agonists or antagonists of the present invention may inhibit chemotactic activity. These molecules could also be used to treat disorders. Thus, polynucleotides or polypeptides, as well as agonists or antagonists of the present invention could be used as an inhibitor of chemotaxis.

Binding Activity

A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules
5 include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide
10 binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially
15 containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal
20 generated by binding to the polypeptide.

Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound
25 with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the
30 polypeptide or by competing with the polypeptide for a substrate.

Additionally, the receptor to which the polypeptide of the present invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand

panning and FACS sorting (Coligan, et al., Current Protocols in Immun., 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

Following fixation and incubation, the slides are subjected to auto-radiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of the polypeptide of the present invention thereby effectively generating agonists and antagonists of the polypeptide of the present invention. *See generally*, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., *et al.*, *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., *et al.*, *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding

polypeptides may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptide of the present invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs), nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

Other preferred fragments are biologically active fragments of the polypeptide of the present invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and ^3H thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of ^3H thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of ^3H thymidine. Both agonist and antagonist compounds may be identified by this procedure.

In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the

present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues.

Therefore, the invention includes a method of identifying compounds which bind to a polypeptide of the invention comprising the steps of: (a) incubating a candidate binding compound with a polypeptide of the present invention; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with a polypeptide of the present invention, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

Targeted Delivery

In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

As discussed herein, polypeptides or antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method

for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

5 In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector
10 systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an
15 inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be
20 used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

25 **Drug Screening**

Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of
30 having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

This invention is particularly useful for screening therapeutic compounds by using the

polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells
5 which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

Thus, the present invention provides methods of screening for drugs or any other
10 agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is
15 separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and
20 is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein. Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known
25 in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention
30 specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

Antisense And Ribozyme (Antagonists)

In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained in the cDNA contained in the related cDNA clone identified in Table 1. In one embodiment, antisense sequence is generated internally, by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, J., *Neurochem.* 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, J., *Neurochem.* 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., *Nucleic Acids Research* 6:3073 (1979); Cooney et al., *Science* 241:456 (1988); and Dervan et al., *Science* 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.

For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl₂, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

For example, the 5' coding portion of a polynucleotide that encodes the polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the

production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding the polypeptide of the present invention or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, *Nature* 29:304-310 (1981)), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., *Cell* 22:787-797 (1980)), the herpes thymidine promoter (Wagner et al., *Proc. Natl. Acad. Sci. U.S.A.* 78:1441-1445 (1981)), the regulatory sequences of the metallothionein gene (Brinster, et al., *Nature* 296:39-42 (1982)), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of the present invention. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

Oligonucleotides that are complementary to the 5' end of the message, e.g., the 5' untranslated sequence up to and including the AUG initiation codon, should work most

efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., 1994, *Nature* 372:333-335. Thus, oligonucleotides complementary to either the 5'- or 3'- non- translated, non-coding regions of polynucleotide sequences described herein could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5'-, 3'- or coding region of mRNA of the present invention, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50 nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556; Lemaitre et al., 1987, *Proc. Natl. Acad. Sci.* 84:648-652; PCT Publication No. WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication No. WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., 1988, *BioTechniques* 6:958-976) or intercalating agents. (See, e.g., Zon, 1988, *Pharm. Res.* 5:539-549). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine,

2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 5 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, 10 and hexose.

In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or 15 analog thereof.

In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641). The oligonucleotide is a 2'-O-methylribose nucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric 20 RNA-DNA analogue (Inoue et al., 1987, FEBS Lett. 215:327-330).

Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides 25 may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. U.S.A. 85:7448-7451), etc.

While antisense nucleotides complementary to the coding region sequence could be used, those complementary to the transcribed untranslated region are most preferred.

30 Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science 247:1222-1225 (1990). While ribozymes that cleave mRNA at

site specific recognition sequences can be used to destroy mRNAs, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5'-UG-3'.

- 5 The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, Nature 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within the nucleotide sequence of SEQ ID NO:X. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA; i.e., to increase efficiency and minimize the
- 10 intracellular accumulation of non-functional mRNA transcripts.

As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding

15 DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

- 20 Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

- The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and
- 25 prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the present invention may also be desirous in cases such as restenosis after balloon angioplasty.

The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

- 30 The antagonist/agonist may also be employed to treat the diseases described herein.

Thus, the invention provides a method of treating disorders or diseases, including but not limited to the disorders or diseases listed throughout this application, associated with

overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

5 **Other Activities**

A polypeptide, polynucleotide, agonist, or antagonist of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. The
10 polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells
15 and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed stimulate neuronal growth and to treat and prevent neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's
20 disease, Parkinson's disease, and AIDS-related complex. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may have the ability to stimulate chondrocyte growth, therefore, they may be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be
25 also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, a polypeptide, polynucleotide,
30 agonist, or antagonist of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues. A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, a polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive disorders), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

A polypeptide, polynucleotide, agonist, or antagonist of the present invention may also be used as a food additive or preservative, such as to increase or decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.

Other Preferred Embodiments

Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X in the range of positions identified as "Start" and "End" in columns 7 and 8 as defined for SEQ ID NO:X in Table 1.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule comprising a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto, and/or the cDNA in the related cDNA clone contained in the deposit, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

Also preferred is a composition of matter comprising a DNA molecule which comprises a cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least
5 50 contiguous nucleotides is included in the nucleotide sequence of an open reading frame sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the
10 deposit.

A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

15 A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a
20 sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and
25 determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected
30 from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a

nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleotide sequence of SEQ ID NO:X; or the cDNA in the related cDNA clone identified in Table 1 which encodes a protein, wherein the method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence of the cDNA in the related cDNA clone contained in the deposit.

Also preferred is the above method for diagnosing a pathological condition which comprises a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the

group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the related cDNA clone contained in the deposit. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

5 Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a DNA microarray or "chip" of at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 40, 50, 100, 150, 200, 250, 300, 500, 1000, 2000, 3000 or 4000 nucleotide sequences, wherein at least one sequence in said DNA microarray or "chip" is at least 95% identical to a sequence of at least 50 contiguous
10 nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X or the complementary strand thereto; and a nucleotide sequence encoded by the cDNA in the cDNA clone referenced in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least
15 90% identical to a sequence of at least about 10 contiguous amino acids in the polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least
20 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a
25 polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and/or a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

30 Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a portion of said polypeptide encoded by the cDNA clone referenced in Table 1; a polypeptide encoded by SEQ ID NO:X; and/or the polypeptide sequence of SEQ ID NO:Y.

5 Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid
10 sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of a polypeptide encoded by the cDNA clone referenced in Table 1.

Further preferred is an isolated antibody which binds specifically to a polypeptide
15 comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone contained in the deposit.

Further preferred is a method for detecting in a biological sample a polypeptide
20 comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1; which method comprises a step of comparing an amino acid sequence of at least one polypeptide molecule
25 in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from
30 said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in

a sequence selected from the group consisting of: a polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a nucleic acid sequence identified in Table 1 encoding a polypeptide, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of:

polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a
5 prokaryotic host.

Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1.

10 Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

15 Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a human protein comprising an amino acid sequence selected from the group consisting of:
20 polypeptide sequence of SEQ ID NO:Y; a polypeptide encoded by SEQ ID NO:X; and a polypeptide encoded by the cDNA in the related cDNA clone referenced in Table 1. The isolated polypeptide produced by this method is also preferred.

Also preferred is a method of treatment of an individual in need of an increased level of a protein activity, which method comprises administering to such an individual a
25 Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to increase the level of said protein activity in said individual.

Also preferred is a method of treatment of an individual in need of a decreased level of a protein activity, which method comprised administering to such an individual a
30 Therapeutic comprising an amount of an isolated polypeptide, polynucleotide, immunogenic fragment or analogue thereof, binding agent, antibody, or antigen binding fragment of the claimed invention effective to decrease the level of said protein activity in said individual.

Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

*Examples**Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample*

5 Each deposited cDNA clone is contained in a plasmid vector. Table 5 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The following correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 5 as being isolated in the vector "Lambda Zap,"
 10 the corresponding deposited clone is in "pBluescript."

| | <u>Vector Used to Construct Library</u> | <u>Corresponding Deposited Plasmid</u> |
|----|---|--|
| | Lambda Zap | pBluescript (pBS) |
| | Uni-Zap XR | pBluescript (pBS) |
| 15 | Zap Express | pBK |
| | lafmid BA | plafmid BA |
| | pSportI | pSportI |
| | pCMVSPORT 2.0 | pCMVSPORT 2.0 |
| | pCMVSPORT 3.0 | pCMVSPORT 3.0 |
| 20 | pCR [®] 2.1 | pCR [®] 2.1 |

Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Alting-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Alting-Mees, M. A. et al., Strategies 5:58-61 (1992)) are commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3
 30

primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

Vectors pSport1, pCMVSPORT 2.0 and pCMVSPORT 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR[®]2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 5, as well as the corresponding plasmid vector sequences designated above.

The deposited material in the sample assigned the ATCC Deposit Number cited by reference to Table 2 and 5 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone referenced in Table 1.

TABLE 5

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|--|---|---------------|--------------|
| HUKA HUKB HUKC HUKD HUKF HUKF HUKG | Human Uterine Cancer | Lambda ZAP II | LP01 |
| HCNA HCNB | Human Colon | Lambda Zap II | LP01 |
| HFFA | Human Fetal Brain, random primed | Lambda Zap II | LP01 |
| HTWA | Resting T-Cell | Lambda ZAP II | LP01 |
| HBQA | Early Stage Human Brain, random primed | Lambda ZAP II | LP01 |
| HLMB HLMF HLMG HLMH HLMJ HLMJ HLMN | breast lymph node CDNA library | Lambda ZAP II | LP01 |
| HCQA HCQB | human colon cancer | Lambda ZAP II | LP01 |
| HMEA HMEC HMEC HMEC HMEF HMEG HMEI HMEJ HMEK HMEI | Human Microvascular Endothelial Cells, fract. A | Lambda ZAP II | LP01 |
| HUSA HUSC | Human Umbilical Vein Endothelial Cells, fract. A | Lambda ZAP II | LP01 |
| HLQA HLQB | Hepatocellular Tumor | Lambda ZAP II | LP01 |
| HHGA HHGB HHGC HHGD | Hemangiopericytoma | Lambda ZAP II | LP01 |
| HSDM | Human Striatum Depression. re-rescue | Lambda ZAP II | LP01 |
| HUSH | H Umbilical Vein Endothelial Cells, fract. A, re-excision | Lambda ZAP II | LP01 |
| HSGS | Salivary gland, subtracted | Lambda ZAP II | LP01 |
| HFXA HFXB HFXC HFXD HFXE HFXF HFXG HFXH | Brain frontal cortex | Lambda ZAP II | LP01 |
| HPQA HPQB HPQC | PERM TF274 | Lambda ZAP II | LP01 |
| HFXJ HFXK | Brain Frontal Cortex, re-excision | Lambda ZAP II | LP01 |
| HCWA HCWB HCWC HCWD HCWE HCWF HCWG HCWH HCWI HCWJ HCWK | CD34 positive cells (Cord Blood) | ZAP Express | LP02 |
| HCUA HCUB HCUC | CD34 depleted Buffy Coat (Cord Blood) | ZAP Express | LP02 |
| HRSM | A-14 cell line | ZAP Express | LP02 |
| HRSA | A1-CELL LINE | ZAP Express | LP02 |
| HCUD HCUE HCUF HCUG HCUH HCUH HCUH | CD34 depleted Buffy Coat (Cord Blood), re-excision | ZAP Express | LP02 |
| HBXE HBXF HBXG | H. Whole Brain #2, re-excision | ZAP Express | LP02 |
| HRLM | L8 cell line | ZAP Express | LP02 |
| HBXA HBXB HBXC HBXD | Human Whole Brain #2 - Oligo dT > 1.5Kb | ZAP Express | LP02 |
| HUDA HUDB HUDC | Testes | ZAP Express | LP02 |
| HHTM HHTN HHTO | H. hypothalamus, fract. A; re-excision | ZAP Express | LP02 |
| HHTL | H. hypothalamus, fract. A | ZAP Express | LP02 |
| HASA HASD | Human Adult Spleen | Uni-ZAP XR | LP03 |
| HFKC HFKD HFKE HFKF HFKG | Human Fetal Kidney | Uni-ZAP XR | LP03 |
| HE8A HE8B HE8C HE8D HE8E HE8F HE8M HE8N | Human 8 Week Whole Embryo | Uni-ZAP XR | LP03 |
| HGBA HGBD HGBE HGBF HGBG HGBH HGBI | Human Gall Bladder | Uni-ZAP XR | LP03 |
| HLHA HLHB HLHC HLHD HLHE HLHF HLHG HLHH HLHQ | Human Fetal Lung III | Uni-ZAP XR | LP03 |
| HPMA HPMB HPMC HPMD HPME HPMF HPMG HPMH | Human Placenta | Uni-ZAP XR | LP03 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|---|--|------------|--------------|
| HPRA HPRB HPRC HPRD | Human Prostate | Uni-ZAP XR | LP03 |
| HSIA HSIC HSID HSIE | Human Adult Small Intestine | Uni-ZAP XR | LP03 |
| HTEA HTEB HTEC HTED HTEE HTEF HTEG HTEH HTEI HTEJ HTEK | Human Testes | Uni-ZAP XR | LP03 |
| HTPA HTPB HTPC HTPD HTPE | Human Pancreas Tumor | Uni-ZAP XR | LP03 |
| HTTA HTTB HTTC HTTD HTTE HTTF | Human Testes Tumor | Uni-ZAP XR | LP03 |
| HAPA HAPB HAPC HAPM | Human Adult Pulmonary | Uni-ZAP XR | LP03 |
| HETA HETB HETC HETD HETE HETF HETG HETH HETI | Human Endometrial Tumor | Uni-ZAP XR | LP03 |
| HHFB HHFC HHFD HHFE HHFF HHFG HHFH HHFI | Human Fetal Heart | Uni-ZAP XR | LP03 |
| HHPB HHPC HHPD HHPE HHPF HHPG HHPH | Human Hippocampus | Uni-ZAP XR | LP03 |
| HCE1 HCE2 HCE3 HCE4 HCE5 HCEB HCEC HCED HCEE HCEF HCEG | Human Cerebellum | Uni-ZAP XR | LP03 |
| HUVB HUV C HUVD HUVE | Human Umbilical Vein, Endo. remake | Uni-ZAP XR | LP03 |
| HSTA HSTB HSTC HSTD | Human Skin Tumor | Uni-ZAP XR | LP03 |
| HTAA HTAB HTAC HTAD HTAE | Human Activated T-Cells | Uni-ZAP XR | LP03 |
| HFEA HFEB HFEC | Human Fetal Epithelium (Skin) | Uni-ZAP XR | LP03 |
| HJPA HJPB HJPC HJPD | HUMAN JURKAT MEMBRANE BOUND POLYSOMES | Uni-ZAP XR | LP03 |
| HESA | Human epithelioid sarcoma | Uni-Zap XR | LP03 |
| HLTA HLTB HLTC HLTD HLTE HLTF | Human T-Cell Lymphoma | Uni-ZAP XR | LP03 |
| HFTA HFTB HFTC HFTD | Human Fetal Dura Mater | Uni-ZAP XR | LP03 |
| HRDA HRDB HRDC HRDD HRDE HRDF | Human Rhabdomyosarcoma | Uni-ZAP XR | LP03 |
| HCAA HCAB HCAC | Cem cells cyclohexamide treated | Uni-ZAP XR | LP03 |
| HRGA HRGB HRGC HRGD | Raji Cells, cyclohexamide treated | Uni-ZAP XR | LP03 |
| HSUA HSUB HSUC HSUM | Supt Cells, cyclohexamide treated | Uni-ZAP XR | LP03 |
| HT4A HT4C HT4D | Activated T-Cells, 12 hrs. | Uni-ZAP XR | LP03 |
| HE9A HE9B HE9C HE9D HE9E HE9F HE9G HE9H HE9M HE9N | Nine Week Old Early Stage Human | Uni-ZAP XR | LP03 |
| HATA HATB HATC HATD HATE | Human Adrenal Gland Tumor | Uni-ZAP XR | LP03 |
| HT5A | Activated T-Cells, 24 hrs. | Uni-ZAP XR | LP03 |
| HFGA HFGM | Human Fetal Brain | Uni-ZAP XR | LP03 |
| HNEA HNEB HNEC HNED HNEE | Human Neutrophil | Uni-ZAP XR | LP03 |
| HBGB HBGD | Human Primary Breast Cancer | Uni-ZAP XR | LP03 |
| HBNA HBNB | Human Normal Breast | Uni-ZAP XR | LP03 |
| HCAS | Cem Cells, cyclohexamide treated, subtra | Uni-ZAP XR | LP03 |
| HHPS | Human Hippocampus, subtracted | pBS | LP03 |
| HKCS HKCU | Human Colon Cancer, subtracted | pBS | LP03 |
| HRGS | Raji cells, cyclohexamide treated, subtracted | pBS | LP03 |
| HSUT | Supt cells, cyclohexamide treated, differentially expressed | pBS | LP03 |
| HT4S | Activated T-Cells, 12 hrs, subtracted | Uni-ZAP XR | LP03 |
| HCDA HCDB HCDC HCDD HCDE | Human Chondrosarcoma | Uni-ZAP XR | LP03 |
| HOAA HOAB HOAC | Human Osteosarcoma | Uni-ZAP XR | LP03 |
| HTLA HTLB HTLC HTLD HTLE | Human adult testis, large inserts | Uni-ZAP XR | LP03 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|--|--|------------|--------------|
| HTLF | | | |
| HLMA HLMC HLMD | Breast Lymph node cDNA library | Uni-ZAP XR | LP03 |
| H6EA H6EB H6EC | HL-60, PMA 4H | Uni-ZAP XR | LP03 |
| HTXA HTXB HTXC HTXD HTXE HTXF HTXG HTXH | Activated T-Cell (12hs)/Thiouridine labelledEco | Uni-ZAP XR | LP03 |
| HNFA HNFB HNFC HNFD HNFE HNFF HNFG HNFH HNFJ | Human Neutrophil, Activated | Uni-ZAP XR | LP03 |
| HTOB HTOC | HUMAN TONSILS, FRACTION 2 | Uni-ZAP XR | LP03 |
| HMGB | Human OB MG63 control fraction I | Uni-ZAP XR | LP03 |
| HOPB | Human OB HOS control fraction I | Uni-ZAP XR | LP03 |
| HORB | Human OB HOS treated (10 nM E2) fraction I | Uni-ZAP XR | LP03 |
| HSVA HSVB HSVC | Human Chronic Synovitis | Uni-ZAP XR | LP03 |
| HROA | HUMAN STOMACH | Uni-ZAP XR | LP03 |
| HBJA HBJB HBJC HBJD HBJE HBJF HBJG HBJH HBJI HBJJ HBJK | HUMAN B CELL LYMPHOMA | Uni-ZAP XR | LP03 |
| HCRA HCRB HCRC | human corpus colosum | Uni-ZAP XR | LP03 |
| HODA HODB HODC HODD | human ovarian cancer | Uni-ZAP XR | LP03 |
| HDSA | Dermatofibrosarcoma Protuberance | Uni-ZAP XR | LP03 |
| HMWA HMWB HMWC HMWD HMWE HMWF HMWG HMWH HMWI HMWJ | Bone Marrow Cell Line (RS4;11) | Uni-ZAP XR | LP03 |
| HSOA | stomach cancer (human) | Uni-ZAP XR | LP03 |
| HERA | SKIN | Uni-ZAP XR | LP03 |
| HMDA | Brain-medulloblastoma | Uni-ZAP XR | LP03 |
| HGLA HGLB HGLD | Glioblastoma | Uni-ZAP XR | LP03 |
| HEAA | H. Atrophic Endometrium | Uni-ZAP XR | LP03 |
| HBCA HBCB | H. Lymph node breast Cancer | Uni-ZAP XR | LP03 |
| HPWT | Human Prostate BPH, re-excision | Uni-ZAP XR | LP03 |
| HFVG HFVH HFVI | Fetal Liver, subtraction II | pBS | LP03 |
| HNFI | Human Neutrophils, Activated, re- excision | pBS | LP03 |
| HBMB HBMC HBMD | Human Bone Marrow, re-excision | pBS | LP03 |
| HKML HKMM HKMN | H. Kidney Medulla, re-excision | pBS | LP03 |
| HKIX HKIY | H. Kidney Cortex, subtracted | pBS | LP03 |
| HADT | H. Amygdala Depression, subtracted | pBS | LP03 |
| H6AS | HL-60, untreated, subtracted | Uni-ZAP XR | LP03 |
| H6ES | HL-60, PMA 4H, subtracted | Uni-ZAP XR | LP03 |
| H6BS | HL-60, RA 4h, Subtracted | Uni-ZAP XR | LP03 |
| H6CS | HL-60, PMA 1d, subtracted | Uni-ZAP XR | LP03 |
| HTXJ HTXK | Activated T-cell(12h)/Thiouridine-re- excision | Uni-ZAP XR | LP03 |
| HMSA HMSB HMSC HMSE HMSE HMSF HMSG HMSH HMSI HMSJ HMSK | Monocyte activated | Uni-ZAP XR | LP03 |
| HAGA HAGB HAGC HAGD HAGE HAGF | Human Amygdala | Uni-ZAP XR | LP03 |
| HSRA HSRB HSRE | STROMAL -OSTEOCLASTOMA | Uni-ZAP XR | LP03 |
| HSRD HSRF HSRG HSRH | Human Osteoclastoma Stromal Cells - unamplified | Uni-ZAP XR | LP03 |
| HSQA HSQB HSQC HSQD HSQE | Stromal cell TF274 | Uni-ZAP XR | LP03 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|---|---|------------|--------------|
| HSQF HSQG | | | |
| HSKA HSKB HSKC HSKD HSKE HSKF HSKZ | Smooth muscle, serum treated | Uni-ZAP XR | LP03 |
| HSLA HSLB HSLC HSLD HSLE HSLF HSLG | Smooth muscle, control | Uni-ZAP XR | LP03 |
| HSDA HSDD HSDE HSDF HSDG HSDH | Spinal cord | Uni-ZAP XR | LP03 |
| HPWS | Prostate-BPH subtracted II | pBS | LP03 |
| HSKW HSKX HSKY | Smooth Muscle- HASTE normalized | pBS | LP03 |
| HFPB HFPC HFPD | H. Frontal cortex, epileptic, re-excision | Uni-ZAP XR | LP03 |
| HSDI HSDJ HSDK | Spinal Cord, re-excision | Uni-ZAP XR | LP03 |
| HSKN HSKO | Smooth Muscle Serum Treated, Norm | pBS | LP03 |
| HSKG HSKH HSKI | Smooth muscle, serum induced, re-exc | pBS | LP03 |
| HFCA HFCB HFCC HFCD HFCE HFCF | Human Fetal Brain | Uni-ZAP XR | LP04 |
| HPTA HPTB HPTD | Human Pituitary | Uni-ZAP XR | LP04 |
| HTHB HTHC HTHD | Human Thymus | Uni-ZAP XR | LP04 |
| HE6B HE6C HE6D HE6E HE6F HE6G HE6S | Human Whole Six Week Old Embryo | Uni-ZAP XR | LP04 |
| HSSA HSSB HSSC HSSD HSSE HSSF HSSG HSSH HSSI HSSJ HSSK HE7T | Human Synovial Sarcoma | Uni-ZAP XR | LP04 |
| | 7 Week Old Early Stage Human, subtracted | Uni-ZAP XR | LP04 |
| HEPA HEPB HEPC | Human Epididymus | Uni-ZAP XR | LP04 |
| HSNA HSNB HSNC HSNM HSNN | Human Synovium | Uni-ZAP XR | LP04 |
| HPFB HPFC HPFD HPFE | Human Prostate Cancer, Stage C fraction | Uni-ZAP XR | LP04 |
| HE2A HE2D HE2E HE2H HE2I HE2M HE2N HE2O | 12 Week Old Early Stage Human | Uni-ZAP XR | LP04 |
| HE2B HE2C HE2F HE2G HE2P HE2Q | 12 Week Old Early Stage Human, II | Uni-ZAP XR | LP04 |
| HPTS HPTT HPTU | Human Pituitary, subtracted | Uni-ZAP XR | LP04 |
| HAUA HAUB HAUC | Amniotic Cells - TNF induced | Uni-ZAP XR | LP04 |
| HAQA HAQB HAQC HAQD | Amniotic Cells - Primary Culture | Uni-ZAP XR | LP04 |
| HUTA HWTB HWTC | wilm's tumor | Uni-ZAP XR | LP04 |
| HBSD | Bone Cancer, re-excision | Uni-ZAP XR | LP04 |
| HSGB | Salivary gland, re-excision | Uni-ZAP XR | LP04 |
| HSJA HSJB HSJC | Smooth muscle-ILb induced | Uni-ZAP XR | LP04 |
| HSXA HSXB HSXC HSXD | Human Substantia Nigra | Uni-ZAP XR | LP04 |
| HSJA HSJB HSJC | Smooth muscle, IL1b induced | Uni-ZAP XR | LP04 |
| HOUA HOUB HOU C HOUD HOU E | Adipocytes | Uni-ZAP XR | LP04 |
| HPWA HPWB HPWC HPWD HPWE | Prostate BPH | Uni-ZAP XR | LP04 |
| HELA HELB HELC HELD HELE HELF HELG HELH | Endothelial cells-control | Uni-ZAP XR | LP04 |
| HEMA HEMB HEMC HEMD HEME HEMF HEMG HEMH | Endothelial-induced | Uni-ZAP XR | LP04 |
| HBIA HBIB HBIC | Human Brain, Striatum | Uni-ZAP XR | LP04 |
| HHS A HHSB HHS C HHS D HHS E | Human Hypothalamus, Schizophrenia | Uni-ZAP XR | LP04 |
| HNGA HNGB HNGC HNGD HNGE HNGF HNGG HNGH HNGI HNGJ | neutrophils control | Uni-ZAP XR | LP04 |
| HNHA HNHB HNHC HNHD HNHE HNHF HNHG HNHH HNHI HNHI | Neutrophils IL-1 and LPS induced | Uni-ZAP XR | LP04 |
| HSDB HSDC | STRIATUM DEPRESSION | Uni-ZAP XR | LP04 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|---|--|---------------|--------------|
| HHPT | Hypothalamus | Uni-ZAP XR | LP04 |
| HSAT HSAU HSAV HSAW HSAX HSAY HSAZ | Anergic T-cell | Uni-ZAP XR | LP04 |
| HBMS HBMT HBMU HBMV HBMW HBMX | Bone marrow | Uni-ZAP XR | LP04 |
| HOEA HOEB HOEC HOED HOEE HOEF HOEJ | Osteoblasts | Uni-ZAP XR | LP04 |
| HAIA HAIB HAIC HAID HAIE HAIF | Epithelial-TNF α and INF induced | Uni-ZAP XR | LP04 |
| HTGA HTGB HTGC HTGD | Apoptotic T-cell | Uni-ZAP XR | LP04 |
| HMCA HMCB HMCC HMCD HMCE | Macrophage-oxLDL | Uni-ZAP XR | LP04 |
| HMAA HMAB HMAB HMAD HMAE HMAF HMAG | Macrophage (GM-CSF treated) | Uni-ZAP XR | LP04 |
| HPHA | Normal Prostate | Uni-ZAP XR | LP04 |
| HP1A HP1B HP1C | LNCAP prostate cell line | Uni-ZAP XR | LP04 |
| HP1A HP1B HP1C | PC3 Prostate cell line | Uni-ZAP XR | LP04 |
| HOSE HOSF HOSG | Human Osteoclastoma, re-excision | Uni-ZAP XR | LP04 |
| HTGE HTGF | Apoptotic T-cell, re-excision | Uni-ZAP XR | LP04 |
| HMAJ HMAK | H Macrophage (GM-CSF treated), re-excision | Uni-ZAP XR | LP04 |
| HACB HACC HACD | Human Adipose Tissue, re-excision | Uni-ZAP XR | LP04 |
| HFPA | H. Frontal Cortex, Epileptic | Uni-ZAP XR | LP04 |
| HFAA HFAB HFAC HFAD HFAE | Alzheimers, spongy change | Uni-ZAP XR | LP04 |
| HFAM | Frontal Lobe, Dementia | Uni-ZAP XR | LP04 |
| HMIA HMIB HMIC | Human Manic Depression Tissue | Uni-ZAP XR | LP04 |
| HTSA HTSE HTSF HTSG HTSH | Human Thymus | pBS | LP05 |
| HPBA HPBB HPBC HPBD HPBE | Human Pineal Gland | pBS | LP05 |
| HSAA HSAB HSAC | HSA 172 Cells | pBS | LP05 |
| HSBA HSBB HSBC HSBM | HSC172 cells | pBS | LP05 |
| HJAA HJAB HJAC HJAD | Jurkat T-cell G1 phase | pBS | LP05 |
| HJBA HJBB HJBC HJBD | Jurkat T-Cell, S phase | pBS | LP05 |
| HAFA HAFB | Aorta endothelial cells + TNF- α | pBS | LP05 |
| HAWA HAWB HAWC | Human White Adipose | pBS | LP05 |
| HTNA HTNB | Human Thyroid | pBS | LP05 |
| HONA | Normal Ovary, Premenopausal | pBS | LP05 |
| HARA HARB | Human Adult Retina | pBS | LP05 |
| HLJA HLJB | Human Lung | pCMVSPORT 1 | LP06 |
| HOFM HOFN HOFO | H. Ovarian Tumor, II, OV5232 | pCMVSPORT 2.0 | LP07 |
| HOGA HOGB HOGC | OV 10-3-95 | pCMVSPORT 2.0 | LP07 |
| HCGL | CD34+cells, II | pCMVSPORT 2.0 | LP07 |
| HDLA | Hodgkin's Lymphoma I | pCMVSPORT 2.0 | LP07 |
| HDTA HDTB HDTC HDTD HDTE | Hodgkin's Lymphoma II | pCMVSPORT 2.0 | LP07 |
| HKAA HKAB HKAC HKAD HKAE HKAF HKAG HKAH | Keratinocyte | pCMVSPORT2.0 | LP07 |
| HCIM | CAPFINDER, Crohn's Disease, lib 2 | pCMVSPORT 2.0 | LP07 |
| HKAL | Keratinocyte, lib 2 | pCMVSPORT2.0 | LP07 |
| HKAT | Keratinocyte, lib 3 | pCMVSPORT2.0 | LP07 |
| HNDA | Nasal polyps | pCMVSPORT2.0 | LP07 |
| HDRA | H. Primary Dendritic Cells, lib 3 | pCMVSPORT2.0 | LP07 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|--|--|--------------|--------------|
| HOHA HOHB HOHC | Human Osteoblasts II | pCMVSPORT2.0 | LP07 |
| HLDA HLDB HLDC | Liver, Hepatoma | pCMVSPORT3.0 | LP08 |
| HLDN HLDO HLDP | Human Liver, normal | pCMVSPORT3.0 | LP08 |
| HMTA | pBMC stimulated w/ poly I/C | pCMVSPORT3.0 | LP08 |
| HNTA | NTERA2, control | pCMVSPORT3.0 | LP08 |
| HDP A HDPB HDP C HDPD HDPF HDPG HDPH HDPI HDPJ HDPK | Primary Dendritic Cells, lib 1 | pCMVSPORT3.0 | LP08 |
| HDP M HDPN HDPO HDPP | Primary Dendritic cells, frac 2 | pCMVSPORT3.0 | LP08 |
| HMUA HMUB HMUC | Myeloid Progenitor Cell Line | pCMVSPORT3.0 | LP08 |
| HHEA HHEB HHEC HHED | T Cell helper I | pCMVSPORT3.0 | LP08 |
| HHEM HHEN HHEO HHFP | T cell helper II | pCMVSPORT3.0 | LP08 |
| HEQA HEQB HEQC | Human endometrial stromal cells | pCMVSPORT3.0 | LP08 |
| HJMA HJMB | Human endometrial stromal cells-treated with progesterone | pCMVSPORT3.0 | LP08 |
| HSWA HSWB HSWC | Human endometrial stromal cells-treated with estradiol | pCMVSPORT3.0 | LP08 |
| HSYA HSYB HSYC | Human Thymus Stromal Cells | pCMVSPORT3.0 | LP08 |
| HLWA HLWB HLWC | Human Placenta | pCMVSPORT3.0 | LP08 |
| HRAA HRAB HRAC | Rejected Kidney, lib 4 | pCMVSPORT3.0 | LP08 |
| HMTM | PCR, pBMC I/C treated | PCR II | LP09 |
| HMJA | H. Meningioma, M6 | pSport 1 | LP10 |
| HMKA HMKB HMKC HMKD HMKE | H. Meningioma, M1 | pSport 1 | LP10 |
| HUSG HUSI | Human umbilical vein endothelial cells, IL-4 induced | pSport 1 | LP10 |
| HUSX HUSY | Human Umbilical Vein Endothelial Cells, uninduced | pSport 1 | LP10 |
| HOFA | Ovarian Tumor I, OV5232 | pSport 1 | LP10 |
| HCFA HCFB HCFC HCFC | T-Cell PHA 16 hrs | pSport 1 | LP10 |
| HCFL HCFM HCFN HCFO | T-Cell PHA 24 hrs | pSport 1 | LP10 |
| HADA HADC HADD HADE HADF HADG | Human Adipose | pSport 1 | LP10 |
| HOVA HOVB HOVC | Human Ovary | pSport 1 | LP10 |
| HTWB HTWC HTWD HTWE HTWF | Resting T-Cell Library, II | pSport 1 | LP10 |
| HMMA | Spleen metastatic melanoma | pSport 1 | LP10 |
| HLYA HLYB HLYC HLYD HLYE | Spleen, Chronic lymphocytic leukemia | pSport 1 | LP10 |
| HCGA | CD34+ cell, I | pSport 1 | LP10 |
| HEOM HEON | Human Eosinophils | pSport 1 | LP10 |
| HTDA | Human Tonsil, Lib 3 | pSport 1 | LP10 |
| HSPA | Salivary Gland, Lib 2 | pSport 1 | LP10 |
| HCHA HCHB HCHC | Breast Cancer cell line, MDA 36 | pSport 1 | LP10 |
| HCHM HCHN | Breast Cancer Cell line, angiogenic | pSport 1 | LP10 |
| HCIA | Crohn's Disease | pSport 1 | LP10 |
| HDAA HDAB HDAC | HEL cell line | pSport 1 | LP10 |
| HABA | Human Astrocyte | pSport 1 | LP10 |
| HUFA HUFB HUFC | Ulcerative Colitis | pSport 1 | LP10 |
| HNTM | NTERA2 + retinoic acid, 14 days | pSport 1 | LP10 |
| HDQA | Primary Dendritic cells, CapFinder2, frac I | pSport 1 | LP10 |
| HDQM | Primary Dendritic Cells, CapFinder, frac | pSport 1 | LP10 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|----------------------------|--|---------------|--------------|
| | 2 | | |
| HLDX | Human Liver, normal.CapFinder | pSport 1 | LP10 |
| HULA HULB HULC | Human Dermal Endothelial Cells.untreated | pSport1 | LP10 |
| HUMA | Human Dermal Endothelial cells.treated | pSport1 | LP10 |
| HCJA | Human Stromal Endometrial fibroblasts, untreated | pSport1 | LP10 |
| HCJM | Human Stromal endometrial fibroblasts, treated w/ estradiol | pSport1 | LP10 |
| HEDA | Human Stromal endometrial fibroblasts, treated with progesterone | pSport1 | LP10 |
| HFNA | Human ovary tumor cell OV350721 | pSport1 | LP10 |
| HKGA HKGB HKGC HKGD | Merkel Cells | pSport1 | LP10 |
| HISA HISB HISC | Pancreas Islet Cell Tumor | pSport1 | LP10 |
| HLSA | Skin, burned | pSport1 | LP10 |
| HBZA | Prostate.BPH, Lib 2 | pSport 1 | LP10 |
| HBZS | Prostate BPH.Lib 2. subtracted | pSport 1 | LP10 |
| HFIA HFIB HFIC | Synovial Fibroblasts (control) | pSport 1 | LP10 |
| HFIH HFII HFIJ | Synovial hypoxia | pSport 1 | LP10 |
| HFIT HFIU HFIV | Synovial IL-1/TNF stimulated | pSport 1 | LP10 |
| HGCA | Messangial cell. frac 1 | pSport1 | LP10 |
| HMVA HMVB HMVC | Bone Marrow Stromal Cell. untreated | pSport1 | LP10 |
| HFIX HFII HFIZ | Synovial Fibroblasts (III/TNF), sub | pSport1 | LP10 |
| HFOX HFOY HFOZ | Synovial hypoxia-RSF subtracted | pSport1 | LP10 |
| HMQA HMQB HMQC HMQD | Human Activated Monocytes | Uni-ZAP XR | LP11 |
| HLIA HLIB HLIC | Human Liver | pCMVSPORT 1 | LP012 |
| HHBA HHBB HHBC HHBD HHBE | Human Heart | pCMVSPORT 1 | LP012 |
| HBBA HBBB | Human Brain | pCMVSPORT 1 | LP012 |
| HLJA HLJB HLJC HLJD HLJE | Human Lung | pCMVSPORT 1 | LP012 |
| HOGA HOGB HOGC | Ovarian Tumor | pCMVSPORT 2.0 | LP012 |
| HTJM | Human Tonsils, Lib 2 | pCMVSPORT 2.0 | LP012 |
| HAMF HAMG | KMH2 | pCMVSPORT 3.0 | LP012 |
| HAJA HAJB HAJC | L428 | pCMVSPORT 3.0 | LP012 |
| HWBA HWBB HWBC HWBD HWBE | Dendritic cells, pooled | pCMVSPORT 3.0 | LP012 |
| HWAA HWAB HWAC HWAD HWAE | Human Bone Marrow, treated | pCMVSPORT 3.0 | LP012 |
| HYAA HYAB HYAC | B Cell lymphoma | pCMVSPORT 3.0 | LP012 |
| HWHG HWHH HWHI | Healing groin wound, 6.5 hours post incision | pCMVSPORT 3.0 | LP012 |
| HWHP HWHQ HWHR | Healing groin wound; 7.5 hours post incision | pCMVSPORT 3.0 | LP012 |
| HARM | Healing groin wound - zero hr post-incision (control) | pCMVSPORT 3.0 | LP012 |
| HBIM | Olfactory epithelium; nasalcavity | pCMVSPORT 3.0 | LP012 |
| HWDA | Healing Abdomen wound; 70&90 min post incision | pCMVSPORT 3.0 | LP012 |
| HWEA | Healing Abdomen Wound;15 days post incision | pCMVSPORT 3.0 | LP012 |
| HWJA | Healing Abdomen Wound;21&29 days | pCMVSPORT 3.0 | LP012 |
| HNAL | Human Tongue, frac 2 | pSport1 | LP012 |
| HMJA | H. Meningima, M6 | pSport1 | LP012 |
| HMKA HMKB HMKC HMKE | H. Meningima, M1 | pSport1 | LP012 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|----------------------------|---|-----------------|--------------|
| HOFA | Ovarian Tumor I, OV5232 | pSport I | LP012 |
| HCFA HCFB HCFC HCFC | T-Cell PHA 16 hrs | pSport I | LP012 |
| HCFL HCFM HCFN HCFO | T-Cell PHA 24 hrs | pSport I | LP012 |
| HMAA HMMB HMMC | Spleen metastatic melanoma | pSport I | LP012 |
| HTDA | Human Tonsil, Lib 3 | pSport I | LP012 |
| HDBA | Human Fetal Thymus | pSport I | LP012 |
| HDDA | Pericardium | pSport I | LP012 |
| HBZA | Prostate, BPH, Lib 2 | pSport I | LP012 |
| HWCA | Larynx tumor | pSport I | LP012 |
| HWKA | Normal lung | pSport I | LP012 |
| HSMB | Bone marrow stroma, treated | pSport I | LP012 |
| HBHM | Normal trachea | pSport I | LP012 |
| HLFC | Human Larynx | pSport I | LP012 |
| HLRB | Siebben Polypsis | pSport I | LP012 |
| HNIA | Mammary Gland | pSport I | LP012 |
| HNJB | Palate carcinoma | pSport I | LP012 |
| HNKA | Palate normal | pSport I | LP012 |
| HMZA | Pharynx carcinoma | pSport I | LP012 |
| HABG | Cheek Carcinoma | pSport I | LP012 |
| HMZM | Pharynx Carcinoma | pSport I | LP012 |
| HDRM | Larynx Carcinoma | pSport I | LP012 |
| HVAA | Pancreas normal PCA4 No | pSport I | LP012 |
| HICA | Tongue carcinoma | pSport I | LP012 |
| HUKA HUKB HUKC HUKD HUKE | Human Uterine Cancer | Lambda ZAP II | LP013 |
| HFFA | Human Fetal Brain, random primed | Lambda ZAP II | LP013 |
| HTUA | Activated T-cell labeled with 4-thioluri | Lambda ZAP II | LP013 |
| HBQA | Early Stage Human Brain, random primed | Lambda ZAP II | LP013 |
| HMEB | Human microvascular Endothelial cells, fract. B | Lambda ZAP II | LP013 |
| HUSH | Human Umbilical Vein Endothelial cells, fract. A, re-excision | Lambda ZAP II | LP013 |
| HLQC HLQD | Hepatocellular tumor, re-excision | Lambda ZAP II | LP013 |
| HTWJ HTWK HTWL | Resting T-cell, re-excision | Lambda ZAP II | LP013 |
| HF6S | Human Whole 6 week Old Embryo (II), subt | pBluescript | LP013 |
| HHPS | Human Hippocampus, subtracted | pBluescript | LP013 |
| HLIS | LNCAP, differential expression | pBluescript | LP013 |
| HLHS HLHT | Early Stage Human Lung, Subtracted | pBluescript | LP013 |
| HSUS | Supt cells, cyclohexamide treated, subtracted | pBluescript | LP013 |
| HSUT | Supt cells, cyclohexamide treated, differentially expressed | pBluescript | LP013 |
| HSDS | H. Striatum Depression, subtracted | pBluescript | LP013 |
| HPTZ | Human Pituitary, Subtracted VII | pBluescript | LP013 |
| HSDX | H. Striatum Depression, subt II | pBluescript | LP013 |
| HSDZ | H. Striatum Depression, subt | pBluescript | LP013 |
| HPBA HPBB HPBC HPBD HPBE | Human Pineal Gland | pBluescript SK- | LP013 |
| HRTA | Colorectal Tumor | pBluescript SK- | LP013 |
| HSBA HSBB HSBC HSBM | HSC172 cells | pBluescript SK- | LP013 |
| HJAA HJAB HJAC HJAD | Jurkat T-cell G1 phase | pBluescript SK- | LP013 |
| HJBA HJBB HJBC HJBD | Jurkat T-cell, S1 phase | pBluescript SK- | LP013 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|----------------------------|---|-----------------|--------------|
| HTNA HTNB | Human Thyroid | pBluescript SK- | LP013 |
| HAHA HAHB | Human Adult Heart | Uni-ZAP XR | LP013 |
| HE6A | Whole 6 week Old Embryo | Uni-ZAP XR | LP013 |
| HFCA HFCB HFCC HFCD HFCE | Human Fetal Brain | Uni-ZAP XR | LP013 |
| HFKE HFKE HFKE HFKE HFKE | Human Fetal Kidney | Uni-ZAP XR | LP013 |
| HGBA HGBD HGBE HGBF HGBG | Human Gall Bladder | Uni-ZAP XR | LP013 |
| HPRA HPRB HPRC HPRD | Human Prostate | Uni-ZAP XR | LP013 |
| HTEA HTEB HTEC HTEC HTEC | Human Testes | Uni-ZAP XR | LP013 |
| HTTA HTTB HTTC HTTD HTTE | Human Testes Tumor | Uni-ZAP XR | LP013 |
| HYBA HYBB | Human Fetal Bone | Uni-ZAP XR | LP013 |
| HFLA | Human Fetal Liver | Uni-ZAP XR | LP013 |
| HHFB HHFC HHFD HHFE HHFF | Human Fetal Heart | Uni-ZAP XR | LP013 |
| HUVB HUVB HUVB HUVB | Human Umbilical Vein, End. remake | Uni-ZAP XR | LP013 |
| HTHB HTHC HTHD | Human Thymus | Uni-ZAP XR | LP013 |
| HSTA HSTB HSTC HSTD | Human Skin Tumor | Uni-ZAP XR | LP013 |
| HTAA HTAB HTAC HTAD HTAE | Human Activated T-cells | Uni-ZAP XR | LP013 |
| HFEA HFEB HFEC | Human Fetal Epithelium (skin) | Uni-ZAP XR | LP013 |
| HJPA HJPB HJPC HJPD | Human Jurkat Membrane Bound Polysomes | Uni-ZAP XR | LP013 |
| HESA | Human Epithelioid Sarcoma | Uni-ZAP XR | LP013 |
| HALS | Human Adult Liver, Subtracted | Uni-ZAP XR | LP013 |
| HFTA HFTB HFTC HFTD | Human Fetal Dura Mater | Uni-ZAP XR | LP013 |
| HCAA HCAB HCAC | Cem cells, cyclohexamide treated | Uni-ZAP XR | LP013 |
| HRGA HRGB HRGC HRGD | Raji Cells, cyclohexamide treated | Uni-ZAP XR | LP013 |
| HE9A HE9B HE9C HE9D HE9E | Nine Week Old Early Stage Human | Uni-ZAP XR | LP013 |
| HSFA | Human Fibrosarcoma | Uni-ZAP XR | LP013 |
| HATA HATB HATC HATD HATE | Human Adrenal Gland Tumor | Uni-ZAP XR | LP013 |
| HTRA | Human Trachea Tumor | Uni-ZAP XR | LP013 |
| HE2A HE2D HE2E HE2H HE2I | 12 Week Old Early Stage Human | Uni-ZAP XR | LP013 |
| HE2B HE2C HE2F HE2G HE2P | 12 Week Old Early Stage Human, II | Uni-ZAP XR | LP013 |
| HNEA HNEB HNEC HNED HNEE | Human Neutrophil | Uni-ZAP XR | LP013 |
| HBGA | Human Primary Breast Cancer | Uni-ZAP XR | LP013 |
| HPTS HPTT HPTU | Human Pituitary, subtracted | Uni-ZAP XR | LP013 |
| HMQA HMQB HMQC HMQD | Human Activated Monocytes | Uni-ZAP XR | LP013 |
| HOAA HOAB HOAC | Human Osteosarcoma | Uni-ZAP XR | LP013 |
| HTOA HTOD HTOE HTOF HTOG | human tonsils | Uni-ZAP XR | LP013 |
| HMGB | Human OB MG63 control fraction I | Uni-ZAP XR | LP013 |
| HOPB | Human OB HOS control fraction I | Uni-ZAP XR | LP013 |
| HOQB | Human OB HOS treated (1 nM E2) fraction I | Uni-ZAP XR | LP013 |
| HAUA HAUB HAUC | Amniotic Cells - TNF induced | Uni-ZAP XR | LP013 |
| HAQA HAQB HAQC HAQD | Amniotic Cells - Primary Culture | Uni-ZAP XR | LP013 |
| HROA HROC | HUMAN STOMACH | Uni-ZAP XR | LP013 |
| HBJA HBJB HBJC HBJD HBJE | HUMAN B CELL LYMPHOMA | Uni-ZAP XR | LP013 |
| HODA HODB HODC HODD | human ovarian cancer | Uni-ZAP XR | LP013 |
| HCPA | Corpus Callosum | Uni-ZAP XR | LP013 |
| HSOA | stomach cancer (human) | Uni-ZAP XR | LP013 |
| HERA | SKIN | Uni-ZAP XR | LP013 |
| HMDA | Brain-medulloblastoma | Uni-ZAP XR | LP013 |
| HGLA HGLB HGLD | Glioblastoma | Uni-ZAP XR | LP013 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|----------------------------|---|---------------|--------------|
| HWTA HWTB HWTC | Wilms' tumor | Uni-ZAP XR | LP013 |
| HIEAA | H. Atrophic Endometrium | Uni-ZAP XR | LP013 |
| HAPN HAPO HAPR HAQO HAPR | Human Adult Pulmonary; re-excision | Uni-ZAP XR | LP013 |
| HLTG HLTH | Human T-cell lymphoma; re-excision | Uni-ZAP XR | LP013 |
| HAHC HAHD HAHE | Human Adult Heart; re-excision | Uni-ZAP XR | LP013 |
| HAGA HAGB HAGC HAGD HAGE | Human Amygdala | Uni-ZAP XR | LP013 |
| HSJA HSHB HSJC | Smooth muscle-IL1b induced | Uni-ZAP XR | LP013 |
| HSJA HSHB HSHC | Smooth muscle, IL1b induced | Uni-ZAP XR | LP013 |
| HPWA HPWB HPWC HPWD HPWE | Prostate BPH | Uni-ZAP XR | LP013 |
| HPJA HPJB HPJC | LNCAP prostate cell line | Uni-ZAP XR | LP013 |
| HPJA HPJB HPJC | PC3 Prostate cell line | Uni-ZAP XR | LP013 |
| HBTA | Bone Marrow Stroma. TNF&LPS ind | Uni-ZAP XR | LP013 |
| HMCF HMCG HMCH HMCJ HMCJ | Macrophage-oxLDL; re-excision | Uni-ZAP XR | LP013 |
| HAGG HAGH HAGI | Human Amygdala; re-excision | Uni-ZAP XR | LP013 |
| HACA | H. Adipose Tissue | Uni-ZAP XR | LP013 |
| HKFB | K562 + PMA (36 hrs); re-excision | ZAP Express | LP013 |
| HCWT HCWU HCWV | CD34 positive cells (cord blood); re-ex | ZAP Express | LP013 |
| HBWA | Whole brain | ZAP Express | LP013 |
| HBXA HBXB HBXC HBXD | Human Whole Brain #2 - Oligo dT > 1.5Kb | ZAP Express | LP013 |
| HAVM | Temporal cortex-Alzheimer | pT-Adv | LP014 |
| HAVT | Hippocampus, Alzheimer Subtracted | pT-Adv | LP014 |
| HHAS | CHME Cell Line | Uni-ZAP XR | LP014 |
| HBJR | Larynx normal | pSport 1 | LP014 |
| HWLE HWLF HWLG HWLH | Colon Normal | pSport 1 | LP014 |
| HCRM HCRN HCRO | Colon Carcinoma | pSport 1 | LP014 |
| HWLI HWLJ HWLK | Colon Normal | pSport 1 | LP014 |
| HWLQ HWLR HWLS HWLT | Colon Tumor | pSport 1 | LP014 |
| HBFM | Gastrocnemius Muscle | pSport 1 | LP014 |
| HBOD HBOE | Quadriceps Muscle | pSport 1 | LP014 |
| HBKD HBKE | Soleus Muscle | pSport 1 | LP014 |
| HCCM | Pancreatic Langerhans | pSport 1 | LP014 |
| HWGA | Larynx carcinoma | pSport 1 | LP014 |
| HWGM HWGN | Larynx carcinoma | pSport 1 | LP014 |
| HWLA HWLB HWLC | Normal colon | pSport 1 | LP014 |
| HWLM HWLN | Colon Tumor | pSport 1 | LP014 |
| HVAM HVAN HVAO | Pancreas Tumor | pSport 1 | LP014 |
| HWGQ | Larynx carcinoma | pSport 1 | LP014 |
| HAQM HAQN | Salivary Gland | pSport 1 | LP014 |
| HASM | Stomach; normal | pSport 1 | LP014 |
| HBCM | Uterus; normal | pSport 1 | LP014 |
| HCDM | Testis; normal | pSport 1 | LP014 |
| HDJM | Brain; normal | pSport 1 | LP014 |
| HEFM | Adrenal Gland; normal | pSport 1 | LP014 |
| HBAA | Rectum normal | pSport 1 | LP014 |
| HFDI | Rectum tumour | pSport 1 | LP014 |
| HGAM | Colon, normal | pSport 1 | LP014 |
| HHMM | Colon, tumour | pSport 1 | LP014 |
| HCLB HCLC | Human Lung Cancer | Lambda Zap II | LP015 |
| HRLA | LI Cell line | ZAP Express | LP015 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|----------------------------|--|-------------------|--------------|
| HHAM | Hypothalamus, Alzheimer's | pCMVSPORT 3.0 | LP015 |
| HKBA | Ku 812F Basophils Line | pSport 1 | LP015 |
| HS2S | Saos2, Dexamethosone Treated | pSport 1 | LP016 |
| HA5A | Lung Carcinoma A549 TNFalpha activated | pSport 1 | LP016 |
| HTFM | TF-1 Cell Line GM-CSF Treated | pSport 1 | LP016 |
| HYAS | Thyroid Tumour | pSport 1 | LP016 |
| HUTS | Larynx Normal | pSport 1 | LP016 |
| HXOA | Larynx Tumor | pSport 1 | LP016 |
| HEAH | Ea.hy 926 cell line | pSport 1 | LP016 |
| HINA | Adenocarcinoma Human | pSport 1 | LP016 |
| HRMA | Lung Mesothelium | pSport 1 | LP016 |
| HLCL | Human Pre-Differentiated Adipocytes | Uni-Zap XR | LP017 |
| HS2A | Saos2 Cells | pSport 1 | LP020 |
| HS2I | Saos2 Cells; Vitamin D3 Treated | pSport 1 | LP020 |
| HUCM | CHME Cell Line, untreated | pSport 1 | LP020 |
| HEPN | Aryepiglottis Normal | pSport 1 | LP020 |
| HPSN | Sinus Piniformis Tumour | pSport 1 | LP020 |
| HNSA | Stomach Normal | pSport 1 | LP020 |
| HNSM | Stomach Tumour | pSport 1 | LP020 |
| HNLA | Liver Normal Met5No | pSport 1 | LP020 |
| HUTA | Liver Tumour Met 5 Tu | pSport 1 | LP020 |
| HOEN | Colon Normal | pSport 1 | LP020 |
| HOCT | Colon Tumor | pSport 1 | LP020 |
| HTNT | Tongue Tumour | pSport 1 | LP020 |
| HLXN | Larynx Normal | pSport 1 | LP020 |
| HLXT | Larynx Tumour | pSport 1 | LP020 |
| HTYN | Thymus | pSport 1 | LP020 |
| HPLN | Placenta | pSport 1 | LP020 |
| HTNG | Tongue Normal | pSport 1 | LP020 |
| HZAA | Thyroid Normal (SDCA2 No) | pSport 1 | LP020 |
| HWES | Thyroid Thyroiditis | pSport 1 | LP020 |
| HFHD | Ficoll Human Stromal Cells, 5Fu treated | pTriplEx2 | LP021 |
| HFHM, HFHN | Ficoll Human Stromal Cells, Untreated | pTriplEx2 | LP021 |
| HPCI | Hep G2 Cells, lambda library | lambda Zap-CMV XR | LP021 |
| HBCA, HBCB, HBCC | H. Lymph node breast Cancer | Uni-ZAP XR | LP021 |
| HCOK | Chondrocytes | pSPORT1 | LP022 |
| HDCA, HDCB, HDCC | Dendritic Cells From CD34 Cells | pSPORT1 | LP022 |
| HDMA, HDMB | CD40 activated monocyte dendritic cells | pSPORT1 | LP022 |
| HDDM, HDDN, HDDO | LPS activated derived dendritic cells | pSPORT1 | LP022 |
| HPCR | Hep G2 Cells, PCR library | lambda Zap-CMV XR | LP022 |
| HAAA, HAAB, HAAC | Lung, Cancer (4005313A3): Invasive Poorly Differentiated Lung Adenocarcinoma | pSPORT1 | LP022 |
| HIPA, HIPB, HIPC | Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic | pSPORT1 | LP022 |
| HOOH, HOOI | Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low | pSPORT1 | LP022 |

| Libraries owned by Catalog | Catalog Description | Vector | ATCC Deposit |
|------------------------------------|--|---------------|--------------|
| | Malignant Pot | | |
| HIDA | Lung, Normal: (4005313 B1) | pSPORT1 | LP022 |
| HUJA.HUJB.HUJC.HUJD.HUJE | B-Cells | pCMVSPORT 3.0 | LP022 |
| HNOA.HNOB.HNOC.HNOD | Ovary, Normal: (9805C040R) | pSPORT1 | LP022 |
| HNLM | Lung, Normal: (4005313 B1) | pSPORT1 | LP022 |
| HSCL | Stromal Cells | pSPORT1 | LP022 |
| HAAX | Lung, Cancer: (4005313 A3) Invasive Poorly-differentiated Metastatic lung adenocarcinoma | pSPORT1 | LP022 |
| HUUA.HUUB.HUUC.HUUD | B-cells (unstimulated) | pTriplEx2 | LP022 |
| HWWA.HWWB.HWWC.HWWD.HWWE.HWWF.HWWG | B-cells (stimulated) | pSPORT1 | LP022 |
| HCCC | Colon, Cancer: (9808C064R) | pCMVSPORT 3.0 | LP023 |
| HPDO HPDP HPDQ HPDR HPD | Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma | pSport 1 | LP023 |
| HPCO HPCP HPCQ HPCT | Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma | pSport 1 | LP023 |
| HOCM HOCO HOCF HOCQ | Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma | pSport 1 | LP023 |
| HCBM HCBN HCBO | Breast, Cancer: (4004943 A5) | pSport 1 | LP023 |
| HNBT HNBH HNBV | Breast, Normal: (4005522B2) | pSport 1 | LP023 |
| HBCP HBCQ | Breast, Cancer: (4005522 A2) | pSport 1 | LP023 |
| HBCJ | Breast, Cancer: (9806C012R) | pSport 1 | LP023 |
| HSAM HSAN | Stromal cells 3.88 | pSport 1 | LP023 |
| HVCA HVCB HVCC HVCD | Ovary, Cancer: (4004332 A2) | pSport 1 | LP023 |
| HSCF HSEN HSEO | Stromal cells (HBM3.18) | pSport 1 | LP023 |
| HSCP HSCQ | stromal cell clone 2.5 | pSport 1 | LP023 |
| HUXA | Breast Cancer: (4005385 A2) | pSport 1 | LP023 |
| HCOM HCON HCOO HCOP HCOQ | Ovary, Cancer (4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma | pSport 1 | LP023 |
| HBNM | Breast, Cancer: (9802C020E) | pSport 1 | LP023 |
| HVVA HVVB HVVC HVVD HVVE | Human Bone Marrow, treated | pSport 1 | LP023 |

Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 5. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to the nucleotide sequence of SEQ ID NO:X.

5 Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with ^{32}P - γ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid
10 mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using
15 Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

Alternatively, two primers of 17-20 nucleotides derived from both ends of the
20 nucleotide sequence of SEQ ID NO:X are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25 μl of reaction mixture with 0.5 μg of the above cDNA template. A convenient reaction mixture is 1.5-5 mM MgCl_2 , 0.01% (w/v) gelatin, 20 μM each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of
25 Taq polymerase. Thirty five cycles of PCR (denaturation at 94°C for 1 min; annealing at 55°C for 1 min; elongation at 72°C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA
30 product.

Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not

limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., Nucleic Acids Res. 21(7):1683-1684 (1993).)

5 Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full
10 length gene.

This above method starts with total RNA isolated from the desired source, although poly-A⁺ RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the
15 RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

This modified RNA preparation is used as a template for first strand cDNA synthesis
20 using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

25

Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide

A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the sequence corresponding to SEQ ID NO:X, according to the method
30 described in Example 1. (See also, Sambrook.)

Example 3: Tissue specific expression analysis

The Human Genome Sciences, Inc. (HGS) database is derived from sequencing tissue specific cDNA libraries. Libraries generated from a particular tissue are selected and the specific tissue expression pattern of EST groups or assembled contigs within these libraries is determined by comparison of the expression patterns of those groups or contigs within the entire database. ESTs which show tissue specific expression are selected.

The original clone from which the specific EST sequence was generated, is obtained from the catalogued library of clones and the insert amplified by PCR using methods known in the art. The PCR product is denatured then transferred in 96 well format to a nylon membrane (Schleicher and Scheull) generating an array filter of tissue specific clones. Housekeeping genes, maize genes, and known tissue specific genes are included on the filters. These targets can be used in signal normalization and to validate assay sensitivity. Additional targets are included to monitor probe length and specificity of hybridization.

Radioactively labeled hybridization probes are generated by first strand cDNA synthesis per the manufacturer's instructions (Life Technologies) from mRNA/RNA samples prepared from the specific tissue being analyzed. The hybridization probes are purified by gel exclusion chromatography, quantitated, and hybridized with the array filters in hybridization bottles at 65°C overnight. The filters are washed under stringent conditions and signals are captured using a Fuji phosphorimager.

Data is extracted using AIS software and following background subtraction, signal normalization is performed. This includes a normalization of filter-wide expression levels between different experimental runs. Genes that are differentially expressed in the tissue of interest are identified and the full length sequence of these clones is generated.

Example 4: Chromosomal Mapping of the Polynucleotides

An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95°C; 1 minute, 56°C; 1 minute, 70°C. This cycle is repeated 32 times followed by one 5 minute

cycle at 70°C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios, Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR
5 fragment in the particular somatic cell hybrid.

Example 5: Bacterial Expression of a Polypeptide

A polynucleotide encoding a polypeptide of the present invention is amplified using
10 PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial
15 expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp^r), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is
20 ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is
25 isolated and confirmed by restriction analysis.

Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.⁶⁰⁰) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto
30 pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4°C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl.

The purified protein is stored at 4°C or frozen at -80°C.

In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (*lacIq*). The origin of replication (*oriC*) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction

sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

The engineered vector could easily be substituted in the above protocol to express
5 protein in a bacterial system.

Example 6: Purification of a Polypeptide from an Inclusion Body

The following alternative method can be used to purify a polypeptide expressed in *E*
10 *coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10°C.

Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10°C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell
15 paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then
20 mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is
25 discarded and the polypeptide containing supernatant is incubated at 4°C overnight to allow further GuHCl extraction.

Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous
30 stirring. The refolded diluted protein solution is kept at 4°C without mixing for 12 hours prior to further purification steps.

To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 μ m membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant A_{280} monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 μ g of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.

Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System

In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under

control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

5 Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

10 Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon, is amplified using the PCR protocol described in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard
15 methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with
20 appropriate restriction enzymes and again purified on a 1% agarose gel.

The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("GeneClean" BIO 101 Inc., La Jolla, Ca.).

25 The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the
30 cloned fragment is confirmed by DNA sequencing.

Five μ g of a plasmid containing the polynucleotide is co-transfected with 1.0 μ g of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA",

Pharmingen, San Diego, CA), using the lipofection method described by Feigner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One μg of BaculoGold™ virus DNA and 5 μg of the plasmid are mixed in a sterile well of a microtiter plate containing 50 μl of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 μl Lipofectin plus 90 μl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27° C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27° C for four days.

After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell culture and baculovirology distributed by Life Technologies Inc., Gaithersburg, page 9-10.) After appropriate incubation, blue stained plaques are picked with the tip of a micropipettor (e.g., Eppendorf). The agar containing the recombinant viruses is then resuspended in a microcentrifuge tube containing 200 μl of Grace's medium and the suspension containing the recombinant baculovirus is used to infect Sf9 cells seeded in 35 mm dishes. Four days later the supernatants of these culture dishes are harvested and then they are stored at 4° C.

To verify the expression of the polypeptide, Sf9 cells are grown in Grace's medium supplemented with 10% heat-inactivated FBS. The cells are infected with the recombinant baculovirus containing the polynucleotide at a multiplicity of infection ("MOI") of about 2. If radiolabeled proteins are desired, 6 hours later the medium is removed and is replaced with SF900 II medium minus methionine and cysteine (available from Life Technologies Inc., Rockville, MD). After 42 hours, 5 μCi of ^{35}S -methionine and 5 μCi ^{35}S -cysteine (available from Amersham) are added. The cells are further incubated for 16 hours and then are harvested by centrifugation. The proteins in the supernatant as well as the intracellular proteins are analyzed by SDS-PAGE followed by autoradiography (if radiolabeled).

Microsequencing of the amino acid sequence of the amino terminus of purified protein may be used to determine the amino terminal sequence of the produced protein.

Example 8: Expression of a Polypeptide in Mammalian Cells

The polypeptide of the present invention can be expressed in a mammalian cell. A typical mammalian expression vector contains a promoter element, which mediates the initiation of transcription of mRNA, a protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription is achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the early promoter of the cytomegalovirus (CMV). However, cellular elements can also be used (e.g., the human actin promoter).

Suitable expression vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC 37152), pSV2dhfr (ATCC 37146), pBC12MI (ATCC 67109), pCMVSPORT 2.0, and pCMVSPORT 3.0. Mammalian host cells that could be used include, human Hela, 293, H9 and Jurkat cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, quail QCI-3 cells, mouse L cells and Chinese hamster ovary (CHO) cells.

Alternatively, the polypeptide can be expressed in stable cell lines containing the polynucleotide integrated into a chromosome. The co-transfection with a selectable marker such as DHFR, gpt, neomycin, hygromycin allows the identification and isolation of the transfected cells.

The transfected gene can also be amplified to express large amounts of the encoded protein. The DHFR (dihydrofolate reductase) marker is useful in developing cell lines that carry several hundred or even several thousand copies of the gene of interest. (See, e.g., Alt, F. W., et al., J. Biol. Chem. 253:1357-1370 (1978); Hamlin, J. L. and Ma, C., Biochem. et Biophys. Acta, 1097:107-143 (1990); Page, M. J. and Sydenham, M. A., Biotechnology 9:64-68 (1991).) Another useful selection marker is the enzyme glutamine synthase (GS) (Murphy et al., Biochem J. 227:277-279 (1991); Bebbington et al., Bio/Technology 10:169-175 (1992). Using these markers, the mammalian cells are grown in selective medium and the cells with the highest resistance are selected. These cell lines contain the amplified gene(s) integrated into a chromosome. Chinese hamster ovary (CHO) and NSO cells are often used

for the production of proteins.

Derivatives of the plasmid pSV2-dhfr (ATCC Accession No. 37146), the expression vectors pC4 (ATCC Accession No. 209646) and pC6 (ATCC Accession No. 209647) contain the strong promoter (LTR) of the Rous Sarcoma Virus (Cullen et al., *Molecular and Cellular Biology*, 438-447 (March, 1985)) plus a fragment of the CMV-enhancer (Boshart et al., *Cell* 41:521-530 (1985).) Multiple cloning sites, e.g., with the restriction enzyme cleavage sites BamHI, XbaI and Asp718, facilitate the cloning of the gene of interest. The vectors also contain the 3' intron, the polyadenylation and termination signal of the rat preproinsulin gene, and the mouse DHFR gene under control of the SV40 early promoter.

Specifically, the plasmid pC6, for example, is digested with appropriate restriction enzymes and then dephosphorylated using calf intestinal phosphates by procedures known in the art. The vector is then isolated from a 1% agarose gel.

A polynucleotide of the present invention is amplified according to the protocol outlined in Example 1. If a naturally occurring signal sequence is used to produce the polypeptide of the present invention, the vector does not need a second signal peptide. Alternatively, if a naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

The amplified fragment is then digested with the same restriction enzyme and purified on a 1% agarose gel. The isolated fragment and the dephosphorylated vector are then ligated with T4 DNA ligase. *E. coli* HB101 or XL-1 Blue cells are then transformed and bacteria are identified that contain the fragment inserted into plasmid pC6 using, for instance, restriction enzyme analysis.

Chinese hamster ovary cells lacking an active DHFR gene is used for transfection. Five μ g of the expression plasmid pC6 or pC4 is cotransfected with 0.5 μ g of the plasmid pSVneo using lipofectin (Felgner et al., *supra*). The plasmid pSV2-neo contains a dominant selectable marker, the *neo* gene from Tn5 encoding an enzyme that confers resistance to a group of antibiotics including G418. The cells are seeded in alpha minus MEM supplemented with 1 mg/ml G418. After 2 days, the cells are trypsinized and seeded in hybridoma cloning plates (Greiner, Germany) in alpha minus MEM supplemented with 10,

25, or 50 ng/ml of methotrexate plus 1 mg/ml G418. After about 10-14 days single clones are trypsinized and then seeded in 6-well petri dishes or 10 ml flasks using different concentrations of methotrexate (50 nM, 100 nM, 200 nM, 400 nM, 800 nM). Clones growing at the highest concentrations of methotrexate are then transferred to new 6-well
5 plates containing even higher concentrations of methotrexate (1 μ M, 2 μ M, 5 μ M, 10 mM, 20 mM). The same procedure is repeated until clones are obtained which grow at a concentration of 100 - 200 μ M. Expression of the desired gene product is analyzed, for instance, by SDS-PAGE and Western blot or by reversed phase HPLC analysis.

10 *Example 9: Protein Fusions*

The polypeptides of the present invention are preferably fused to other proteins. These fusion proteins can be used for a variety of applications. For example, fusion of the present polypeptides to His-tag, HA-tag, protein A, IgG domains, and maltose binding
15 protein facilitates purification. (See Example 5; see also EP A 394,827; Traunecker, et al., Nature 331:84-86 (1988).) Similarly, fusion to IgG-1, IgG-3, and albumin increases the halflife time in vivo. Nuclear localization signals fused to the polypeptides of the present invention can target the protein to a specific subcellular localization, while covalent heterodimer or homodimers can increase or decrease the activity of a fusion protein. Fusion
20 proteins can also create chimeric molecules having more than one function. Finally, fusion proteins can increase solubility and/or stability of the fused protein compared to the non-fused protein. All of the types of fusion proteins described above can be made by modifying the following protocol, which outlines the fusion of a polypeptide to an IgG molecule, or the protocol described in Example 5.

25 Briefly, the human Fc portion of the IgG molecule can be PCR amplified, using primers that span the 5' and 3' ends of the sequence described below. These primers also should have convenient restriction enzyme sites that will facilitate cloning into an expression vector, preferably a mammalian expression vector.

For example, if pC4 (Accession No. 209646) is used, the human Fc portion can be
30 ligated into the BamHI cloning site. Note that the 3' BamHI site should be destroyed. Next, the vector containing the human Fc portion is re-restricted with BamHI, linearizing the

vector, and a polynucleotide of the present invention, isolated by the PCR protocol described in Example 1, is ligated into this BamHI site. Note that the polynucleotide is cloned without a stop codon, otherwise a fusion protein will not be produced.

If the naturally occurring signal sequence is used to produce the polypeptide of the present invention, pC4 does not need a second signal peptide. Alternatively, if the naturally occurring signal sequence is not used, the vector can be modified to include a heterologous signal sequence. (See, e.g., WO 96/34891.)

Human IgG Fc region:

10 GGGATCCGGAGCCCAAATCTTCTGACAAAACCTCACACATGCCCACCGTGCCCAG
CACCTGAATTCGAGGGTGCACCGTCAGTCTTCCTCTTCCCCCAAACCCAAGGA
CACCTCATGATCTCCCGGACTCCTGAGGTCACATGCGTGGTGGTGGACGTAAGC
CACGAAGACCCTGAGGTCAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCAT
AATGCCAAGACAAAGCCGCGGGAGGAGCAGTACAACAGCACGTACCGTGTGGTC
15 AGCGTCCTCACCGTCCTGCACCAGGACTGGCTGAATGGCAAGGAGTACAAGTGC
AAGGTCTCCAACAAAGCCCTCCCAACCCCCATCGAGAAAACCATCTCCAAAGCC
AAAGGGCAGCCCCGAGAACCACAGGTGTACACCCTGCCCCCATCCCGGGATGAG
CTGACCAAGAACCAGGTCAGCCTGACCTGCCTGGTCAAAGGCTTCTATCCAAGC
GACATCGCCGTGGAGTGGGAGAGCAATGGGCAGCCGGAGAACAACACTACAAGAC
20 CACGCCTCCCGTGCTGGACTCCGACGGCTCCTTCTTCTCTACAGCAAGCTCACC
GTGGACAAGAGCAGGTGGCAGCAGGGGAACGTCTTCTCATGCTCCGTGATGCAT
GAGGCTCTGCACAACCACTACACGCAGAAGAGCCTCTCCCTGTCTCCGGGTAAAT
GAGTGCGACGGCCGCGACTCTAGAGGAT (SEQ ID NO:837)

25 *Example 10: Production of an Antibody from a Polypeptide*

a) Hybridoma Technology

The antibodies of the present invention can be prepared by a variety of methods. (See, Current Protocols, Chapter 2.) As one example of such methods, cells expressing polypeptide of the present invention are administered to an animal to induce the production of sera containing polyclonal antibodies. In a preferred method, a preparation of polypeptide

of the present invention is prepared and purified to render it substantially free of natural contaminants. Such a preparation is then introduced into an animal in order to produce polyclonal antisera of greater specific activity.

Monoclonal antibodies specific for polypeptide of the present invention are prepared
5 using hybridoma technology. (Kohler et al., *Nature* 256:495 (1975); Kohler et al., *Eur. J. Immunol.* 6:511 (1976); Kohler et al., *Eur. J. Immunol.* 6:292 (1976); Hammerling et al., in: *Monoclonal Antibodies and T-Cell Hybridomas*, Elsevier, N.Y., pp. 563-681 (1981)). In general, an animal (preferably a mouse) is immunized with polypeptide of the present invention or, more preferably, with a secreted polypeptide of the present invention-
10 expressing cell. Such polypeptide-expressing cells are cultured in any suitable tissue culture medium, preferably in Earle's modified Eagle's medium supplemented with 10% fetal bovine serum (inactivated at about 56°C), and supplemented with about 10 g/l of nonessential amino acids, about 1,000 U/ml of penicillin, and about 100 µg/ml of streptomycin.

The splenocytes of such mice are extracted and fused with a suitable myeloma cell
15 line. Any suitable myeloma cell line may be employed in accordance with the present invention; however, it is preferable to employ the parent myeloma cell line (SP2O), available from the ATCC. After fusion, the resulting hybridoma cells are selectively maintained in HAT medium, and then cloned by limiting dilution as described by Wands et al. (*Gastroenterology* 80:225-232 (1981)). The hybridoma cells obtained through such a
20 selection are then assayed to identify clones which secrete antibodies capable of binding the polypeptide of the present invention.

Alternatively, additional antibodies capable of binding to polypeptide of the present invention can be produced in a two-step procedure using anti-idiotypic antibodies. Such a method makes use of the fact that antibodies are themselves antigens, and therefore, it is
25 possible to obtain an antibody which binds to a second antibody. In accordance with this method, protein specific antibodies are used to immunize an animal, preferably a mouse. The splenocytes of such an animal are then used to produce hybridoma cells, and the hybridoma cells are screened to identify clones which produce an antibody whose ability to bind to the polypeptide of the present invention-specific antibody can be blocked by polypeptide of the
30 present invention. Such antibodies comprise anti-idiotypic antibodies to the polypeptide of the present invention-specific antibody and are used to immunize an animal to induce formation of further polypeptide of the present invention-specific antibodies.

For in vivo use of antibodies in humans, an antibody is "humanized". Such antibodies can be produced using genetic constructs derived from hybridoma cells producing the monoclonal antibodies described above. Methods for producing chimeric and humanized antibodies are known in the art and are discussed herein. (See, for review, Morrison, Science 5 229:1202 (1985); Oi et al., BioTechniques 4:214 (1986); Cabilly et al., U.S. Patent No. 4,816,567; Taniguchi et al., EP 171496; Morrison et al., EP 173494; Neuberger et al., WO 8601533; Robinson et al., WO 8702671; Boulianne et al., Nature 312:643 (1984); Neuberger et al., Nature 314:268 (1985).)

10 **b) Isolation Of Antibody Fragments Directed Against Polypeptide of the Present Invention From A Library Of scFvs**

Naturally occurring V-genes isolated from human PBLs are constructed into a library of antibody fragments which contain reactivities against polypeptide of the present invention to which the donor may or may not have been exposed (see e.g., U.S. Patent 5,885,793 15 incorporated herein by reference in its entirety).

Rescue of the Library. A library of scFvs is constructed from the RNA of human PBLs as described in PCT publication WO 92/01047. To rescue phage displaying antibody fragments, approximately 109 E. coli harboring the phagemid are used to inoculate 50 ml of 2xTY containing 1% glucose and 100 µg/ml of ampicillin (2xTY-AMP-GLU) and grown to 20 an O.D. of 0.8 with shaking. Five ml of this culture is used to inoculate 50 ml of 2xTY-AMP-GLU, 2 x 10⁸ TU of delta gene 3 helper (M13 delta gene III, see PCT publication WO 92/01047) are added and the culture incubated at 37°C for 45 minutes without shaking and then at 37°C for 45 minutes with shaking. The culture is centrifuged at 4000 r.p.m. for 10 min. and the pellet resuspended in 2 liters of 2xTY containing 100 µg/ml ampicillin and 50 25 ug/ml kanamycin and grown overnight. Phage are prepared as described in PCT publication WO 92/01047.

M13 delta gene III is prepared as follows: M13 delta gene III helper phage does not encode gene III protein, hence the phage(mid) displaying antibody fragments have a greater avidity of binding to antigen. Infectious M13 delta gene III particles are made by growing 30 the helper phage in cells harboring a pUC19 derivative supplying the wild type gene III protein during phage morphogenesis. The culture is incubated for 1 hour at 37° C without shaking and then for a further hour at 37°C with shaking. Cells are spun down (IEC-Centra

8,400 r.p.m. for 10 min), resuspended in 300 ml 2xTY broth containing 100 µg ampicillin/ml and 25 µg kanamycin/ml (2xTY-AMP-KAN) and grown overnight, shaking at 37°C. Phage particles are purified and concentrated from the culture medium by two PEG-precipitations (Sambrook et al., 1990), resuspended in 2 ml PBS and passed through a 0.45 µm filter (Minisart NML; Sartorius) to give a final concentration of approximately 10¹³ transducing units/ml (ampicillin-resistant clones).

Panning of the Library. Immunotubes (Nunc) are coated overnight in PBS with 4 ml of either 100 µg/ml or 10 µg/ml of a polypeptide of the present invention. Tubes are blocked with 2% Marvel-PBS for 2 hours at 37°C and then washed 3 times in PBS. Approximately 10¹³ TU of phage is applied to the tube and incubated for 30 minutes at room temperature tumbling on an over and under turntable and then left to stand for another 1.5 hours. Tubes are washed 10 times with PBS 0.1% Tween-20 and 10 times with PBS. Phage are eluted by adding 1 ml of 100 mM triethylamine and rotating 15 minutes on an under and over turntable after which the solution is immediately neutralized with 0.5 ml of 1.0M Tris-HCl, pH 7.4. Phage are then used to infect 10 ml of mid-log E. coli TG1 by incubating eluted phage with bacteria for 30 minutes at 37°C. The E. coli are then plated on TYE plates containing 1% glucose and 100 µg/ml ampicillin. The resulting bacterial library is then rescued with delta gene 3 helper phage as described above to prepare phage for a subsequent round of selection. This process is then repeated for a total of 4 rounds of affinity purification with tube-washing increased to 20 times with PBS, 0.1% Tween-20 and 20 times with PBS for rounds 3 and 4.

Characterization of Binders. Eluted phage from the 3rd and 4th rounds of selection are used to infect E. coli HB 2151 and soluble scFv is produced (Marks, et al., 1991) from single colonies for assay. ELISAs are performed with microtitre plates coated with either 10 pg/ml of the polypeptide of the present invention in 50 mM bicarbonate pH 9.6. Clones positive in ELISA are further characterized by PCR fingerprinting (see, e.g., PCT publication WO 92/01047) and then by sequencing. These ELISA positive clones may also be further characterized by techniques known in the art, such as, for example, epitope mapping, binding affinity, receptor signal transduction, ability to block or competitively inhibit antibody/antigen binding, and competitive agonistic or antagonistic activity.

Example 11: Method of Determining Alterations in a Gene Corresponding to a Polynucleotide

RNA isolated from entire families or individual patients presenting with a phenotype
5 of interest (such as a disease) is be isolated. cDNA is then generated from these RNA
samples using protocols known in the art. (See, Sambrook.) The cDNA is then used as a
template for PCR, employing primers surrounding regions of interest in SEQ ID NO:X;
and/or the nucleotide sequence of the related cDNA in the cDNA clone contained in a
deposited library. Suggested PCR conditions consist of 35 cycles at 95 degrees C for 30
10 seconds; 60-120 seconds at 52-58 degrees C; and 60-120 seconds at 70 degrees C, using
buffer solutions described in Sidransky et al., Science 252:706 (1991).

PCR products are then sequenced using primers labeled at their 5' end with T4
polynucleotide kinase, employing SequiTherm Polymerase. (Epicentre Technologies). The
intron-exon borders of selected exons is also determined and genomic PCR products
15 analyzed to confirm the results. PCR products harboring suspected mutations is then cloned
and sequenced to validate the results of the direct sequencing.

PCR products is cloned into T-tailed vectors as described in Holton et al., Nucleic
Acids Research, 19:1156 (1991) and sequenced with T7 polymerase (United States
Biochemical). Affected individuals are identified by mutations not present in unaffected
20 individuals.

Genomic rearrangements are also observed as a method of determining alterations in
a gene corresponding to a polynucleotide. Genomic clones isolated according to Example 2
are nick-translated with digoxigenindeoxy-uridine 5'-triphosphate (Boehringer Mannheim),
and FISH performed as described in Johnson et al., Methods Cell Biol. 35:73-99 (1991).
25 Hybridization with the labeled probe is carried out using a vast excess of human cot-1 DNA
for specific hybridization to the corresponding genomic locus.

Chromosomes are counterstained with 4,6-diamino-2-phenylidole and propidium
iodide, producing a combination of C- and R-bands. Aligned images for precise mapping are
obtained using a triple-band filter set (Chroma Technology, Brattleboro, VT) in combination
30 with a cooled charge-coupled device camera (Photometrics, Tucson, AZ) and variable
excitation wavelength filters. (Johnson et al., Genet. Anal. Tech. Appl., 8:75 (1991).) Image

collection, analysis and chromosomal fractional length measurements are performed using the ISee Graphical Program System. (Inovision Corporation, Durham, NC.) Chromosome alterations of the genomic region hybridized by the probe are identified as insertions, deletions, and translocations. These alterations are used as a diagnostic marker for an associated disease.

Example 12: Method of Detecting Abnormal Levels of a Polypeptide in a Biological Sample

A polypeptide of the present invention can be detected in a biological sample, and if an increased or decreased level of the polypeptide is detected, this polypeptide is a marker for a particular phenotype. Methods of detection are numerous, and thus, it is understood that one skilled in the art can modify the following assay to fit their particular needs.

For example, antibody-sandwich ELISAs are used to detect polypeptides in a sample, preferably a biological sample. Wells of a microtiter plate are coated with specific antibodies, at a final concentration of 0.2 to 10 ug/ml. The antibodies are either monoclonal or polyclonal and are produced by the method described in Example 10. The wells are blocked so that non-specific binding of the polypeptide to the well is reduced.

The coated wells are then incubated for > 2 hours at RT with a sample containing the polypeptide. Preferably, serial dilutions of the sample should be used to validate results. The plates are then washed three times with deionized or distilled water to remove unbounded polypeptide.

Next, 50 ul of specific antibody-alkaline phosphatase conjugate, at a concentration of 25-400 ng, is added and incubated for 2 hours at room temperature. The plates are again washed three times with deionized or distilled water to remove unbounded conjugate.

Add 75 ul of 4-methylumbelliferyl phosphate (MUP) or p-nitrophenyl phosphate (NPP) substrate solution to each well and incubate 1 hour at room temperature. Measure the reaction by a microtiter plate reader. Prepare a standard curve, using serial dilutions of a control sample, and plot polypeptide concentration on the X-axis (log scale) and fluorescence or absorbance of the Y-axis (linear scale). Interpolate the concentration of the polypeptide in the sample using the standard curve.

Example 13: Formulation

The invention also provides methods of treatment and/or prevention of diseases or disorders (such as, for example, any one or more of the diseases or disorders disclosed
5 herein) by administration to a subject of an effective amount of a Therapeutic. By therapeutic is meant a polynucleotides or polypeptides of the invention (including fragments and variants), agonists or antagonists thereof, and/or antibodies thereto, in combination with a pharmaceutically acceptable carrier type (e.g., a sterile carrier).

The Therapeutic will be formulated and dosed in a fashion consistent with good
10 medical practice, taking into account the clinical condition of the individual patient (especially the side effects of treatment with the Therapeutic alone), the site of delivery, the method of administration, the scheduling of administration, and other factors known to practitioners. The "effective amount" for purposes herein is thus determined by such considerations.

15 As a general proposition, the total pharmaceutically effective amount of the Therapeutic administered parenterally per dose will be in the range of about 1 ug/kg/day to 10 mg/kg/day of patient body weight, although, as noted above, this will be subject to therapeutic discretion. More preferably, this dose is at least 0.01 mg/kg/day, and most preferably for humans between about 0.01 and 1 mg/kg/day for the hormone. If given
20 continuously, the Therapeutic is typically administered at a dose rate of about 1 ug/kg/hour to about 50 ug/kg/hour, either by 1-4 injections per day or by continuous subcutaneous infusions, for example, using a mini-pump. An intravenous bag solution may also be employed. The length of treatment needed to observe changes and the interval following treatment for responses to occur appears to vary depending on the desired effect.

25 Therapeutics can be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray. "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any. The term "parenteral" as used herein refers to modes of
30 administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics are administered orally, rectally, parenterally, intracistemally, intravaginally, intraperitoneally, topically (as by powders, ointments, gels, drops or transdermal patch), buccally, or as an oral or nasal spray.

5 "Pharmaceutically acceptable carrier" refers to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

10 Therapeutics of the invention are also suitably administered by sustained-release systems. Suitable examples of sustained-release Therapeutics include suitable polymeric materials (such as, for example, semi-permeable polymer matrices in the form of shaped articles, e.g., films, or microcapsules), suitable hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, and sparingly soluble derivatives (such as, for example, a sparingly soluble salt).

15 Sustained-release matrices include polylactides (U.S. Pat. No. 3,773,919, EP 58,481), copolymers of L-glutamic acid and gamma-ethyl-L-glutamate (Sidman et al., *Biopolymers* 22:547-556 (1983)), poly (2- hydroxyethyl methacrylate) (Langer et al., *J. Biomed. Mater. Res.* 15:167-277 (1981), and Langer, *Chem. Tech.* 12:98-105 (1982)), ethylene vinyl acetate (Langer et al., *Id.*) or poly-D- (-)-3-hydroxybutyric acid (EP 133,988).

20 Sustained-release Therapeutics also include liposomally entrapped Therapeutics of the invention (*see* generally, Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 317 -327 and 353-365 (1989)). Liposomes containing the Therapeutic are prepared by methods known per se: DE 3,218,121; Epstein et al., *Proc. Natl. Acad. Sci. (USA)* 82:3688-3692 (1985); Hwang et al., *Proc. Natl. Acad. Sci.(USA)* 77:4030-4034 (1980); EP 52,322; EP 36,676; EP 88,046; EP 143,949; EP 142,641; Japanese Pat. Appl. 83-118008; U.S. Pat. Nos. 4,485,045 and 4,544,545; and EP 102,324. Ordinarily, the liposomes are of the small (about 200-800 Angstroms) unilamellar type in which the lipid content is greater than about 30 mol. percent cholesterol, the selected proportion being
30 adjusted for the optimal Therapeutic.

In yet an additional embodiment, the Therapeutics of the invention are delivered by way of a pump (*see* Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987);

Buchwald et al., Surgery 88:507 (1980); Saudek et al., N. Engl. J. Med. 321:574 (1989)).

Other controlled release systems are discussed in the review by Langer (*Science* 249:1527-1533 (1990)).

For parenteral administration, in one embodiment, the Therapeutic is formulated
5 generally by mixing it at the desired degree of purity, in a unit dosage injectable form
(solution, suspension, or emulsion), with a pharmaceutically acceptable carrier, i.e., one that
is non-toxic to recipients at the dosages and concentrations employed and is compatible with
other ingredients of the formulation. For example, the formulation preferably does not
include oxidizing agents and other compounds that are known to be deleterious to the
10 Therapeutic.

Generally, the formulations are prepared by contacting the Therapeutic uniformly and
intimately with liquid carriers or finely divided solid carriers or both. Then, if necessary, the
product is shaped into the desired formulation. Preferably the carrier is a parenteral carrier,
more preferably a solution that is isotonic with the blood of the recipient. Examples of such
15 carrier vehicles include water, saline, Ringer's solution, and dextrose solution. Non-aqueous
vehicles such as fixed oils and ethyl oleate are also useful herein, as well as liposomes.

The carrier suitably contains minor amounts of additives such as substances that
enhance isotonicity and chemical stability. Such materials are non-toxic to recipients at the
dosages and concentrations employed, and include buffers such as phosphate, citrate,
20 succinate, acetic acid, and other organic acids or their salts; antioxidants such as ascorbic
acid; low molecular weight (less than about ten residues) polypeptides, e.g., polyarginine or
tripeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic
polymers such as polyvinylpyrrolidone; amino acids, such as glycine, glutamic acid, aspartic
acid, or arginine; monosaccharides, disaccharides, and other carbohydrates including
25 cellulose or its derivatives, glucose, manose, or dextrans; chelating agents such as EDTA;
sugar alcohols such as mannitol or sorbitol; counterions such as sodium; and/or nonionic
surfactants such as polysorbates, poloxamers, or PEG.

The Therapeutic is typically formulated in such vehicles at a concentration of about
0.1 mg/ml to 100 mg/ml, preferably 1-10 mg/ml, at a pH of about 3 to 8. It will be
30 understood that the use of certain of the foregoing excipients, carriers, or stabilizers will
result in the formation of polypeptide salts.

Any pharmaceutical used for therapeutic administration can be sterile. Sterility is

readily accomplished by filtration through sterile filtration membranes (e.g., 0.2 micron membranes). Therapeutics generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

5 Therapeutics ordinarily will be stored in unit or multi-dose containers, for example, sealed ampoules or vials, as an aqueous solution or as a lyophilized formulation for reconstitution. As an example of a lyophilized formulation, 10-ml vials are filled with 5 ml of sterile-filtered 1% (w/v) aqueous Therapeutic solution, and the resulting mixture is lyophilized. The infusion solution is prepared by reconstituting the lyophilized Therapeutic
10 using bacteriostatic Water-for-Injection.

 The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the Therapeutics of the invention. Associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products,
15 which notice reflects approval by the agency of manufacture, use or sale for human administration. In addition, the Therapeutics may be employed in conjunction with other therapeutic compounds.

 The Therapeutics of the invention may be administered alone or in combination with adjuvants. Adjuvants that may be administered with the Therapeutics of the invention
20 include, but are not limited to, alum, alum plus deoxycholate (ImmunoAg), MTP-PE (Biocine Corp.), QS21 (Genentech, Inc.), BCG, and MPL. In a specific embodiment, Therapeutics of the invention are administered in combination with alum. In another specific embodiment, Therapeutics of the invention are administered in combination with QS-21. Further adjuvants that may be administered with the Therapeutics of the invention include,
25 but are not limited to, Monophosphoryl lipid immunomodulator, AdjuVax 100a, QS-21, QS-18, CRL1005, Aluminum salts, MF-59, and Virosomal adjuvant technology. Vaccines that may be administered with the Therapeutics of the invention include, but are not limited to, vaccines directed toward protection against MMR (measles, mumps, rubella), polio, varicella, tetanus/diphtheria, hepatitis A, hepatitis B, haemophilus influenzae B, whooping
30 cough, pneumonia, influenza, Lyme's Disease, rotavirus, cholera, yellow fever, Japanese encephalitis, poliomyelitis, rabies, typhoid fever, and pertussis. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or

concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous lines into the same individual. Administration "in combination" further includes the separate
5 administration of one of the compounds or agents given first, followed by the second.

The Therapeutics of the invention may be administered alone or in combination with other therapeutic agents. Therapeutic agents that may be administered in combination with the Therapeutics of the invention, include but not limited to, other members of the TNF family, chemotherapeutic agents, antibiotics, steroidal and non-steroidal anti-inflammatories,
10 conventional immunotherapeutic agents, cytokines and/or growth factors. Combinations may be administered either concomitantly, e.g., as an admixture, separately but simultaneously or concurrently; or sequentially. This includes presentations in which the combined agents are administered together as a therapeutic mixture, and also procedures in which the combined agents are administered separately but simultaneously, e.g., as through separate intravenous
15 lines into the same individual. Administration "in combination" further includes the separate administration of one of the compounds or agents given first, followed by the second.

In one embodiment, the Therapeutics of the invention are administered in combination with members of the TNF family. TNF, TNF-related or TNF-like molecules that may be administered with the Therapeutics of the invention include, but are not limited
20 to, soluble forms of TNF-alpha, lymphotoxin-alpha (LT-alpha, also known as TNF-beta), LT-beta (found in complex heterotrimer LT-alpha2-beta), OPGL, FasL, CD27L, CD30L, CD40L, 4-1BBL, DcR3, OX40L, TNF-gamma (International Publication No. WO 96/14328), AIM-I (International Publication No. WO 97/33899), endokine-alpha (International Publication No. WO 98/07880), TR6 (International Publication No. WO
25 98/30694), OPG, and neutrokine-alpha (International Publication No. WO 98/18921, OX40, and nerve growth factor (NGF), and soluble forms of Fas, CD30, CD27, CD40 and 4-1BB, TR2 (International Publication No. WO 96/34095), DR3 (International Publication No. WO 97/33904), DR4 (International Publication No. WO 98/32856), TR5 (International Publication No. WO 98/30693), TR6 (International Publication No. WO 98/30694), TR7
30 (International Publication No. WO 98/41629), TRANK, TR9 (International Publication No. WO 98/56892), TR10 (International Publication No. WO 98/54202), 312C2 (International Publication No. WO 98/06842), and TR12, and soluble forms CD154, CD70, and CD153.

In certain embodiments, Therapeutics of the invention are administered in combination with antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors. Nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, RETROVIR™ (zidovudine/AZT), VIDEX™ (didanosine/ddI), HIVID™ (zalcitabine/ddC), ZERIT™ (stavudine/d4T), EPIVIR™ (lamivudine/3TC), and COMBIVIR™ (zidovudine/lamivudine). Non-nucleoside reverse transcriptase inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, VIRAMUNE™ (nevirapine), RESCRIPTOR™ (delavirdine), and SUSTIVA™ (efavirenz). Protease inhibitors that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, CRIVAN™ (indinavir), NORVIR™ (ritonavir), INVIRASE™ (saquinavir), and VIRACEPT™ (nelfinavir). In a specific embodiment, antiretroviral agents, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and/or protease inhibitors may be used in any combination with Therapeutics of the invention to treat AIDS and/or to prevent or treat HIV infection.

In other embodiments, Therapeutics of the invention may be administered in combination with anti-opportunistic infection agents. Anti-opportunistic agents that may be administered in combination with the Therapeutics of the invention, include, but are not limited to, TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, ATOVAQUONE™, ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, ETHAMBUTOL™, RIFABUTIN™, CLARITHROMYCIN™, AZITHROMYCIN™, GANCICLOVIR™, FOSCARNET™, CIDOFOVIR™, FLUCONAZOLE™, ITRACONAZOLE™, KETOCONAZOLE™, ACYCLOVIR™, FAMCICLOVIR™, PYRIMETHAMINE™, LEUCOVORIN™, NEUPOGEN™ (filgrastim/G-CSF), and LEUKINE™ (sargramostim/GM-CSF). In a specific embodiment, Therapeutics of the invention are used in any combination with TRIMETHOPRIM-SULFAMETHOXAZOLE™, DAPSONE™, PENTAMIDINE™, and/or ATOVAQUONE™ to prophylactically treat or prevent an opportunistic *Pneumocystis carinii* pneumonia infection. In another specific embodiment, Therapeutics of the invention are used in any combination with ISONIAZID™, RIFAMPIN™, PYRAZINAMIDE™, and/or ETHAMBUTOL™ to prophylactically treat or

prevent an opportunistic *Mycobacterium avium* complex infection. In another specific embodiment, Therapeutics of the invention are used in any combination with RIFABUTIN™, CLARITHROMYCIN™, and/or AZITHROMYCIN™ to prophylactically treat or prevent an opportunistic *Mycobacterium tuberculosis* infection. In another specific embodiment,

5 Therapeutics of the invention are used in any combination with GANCICLOVIR™, FOSCARNET™, and/or CIDOFOVIR™ to prophylactically treat or prevent an opportunistic cytomegalovirus infection. In another specific embodiment, Therapeutics of the invention are used in any combination with FLUCONAZOLE™, ITRACONAZOLE™, and/or KETOCONAZOLE™ to prophylactically treat or prevent an opportunistic fungal infection.

10 In another specific embodiment, Therapeutics of the invention are used in any combination with ACYCLOVIR™ and/or FAMCICOLVIR™ to prophylactically treat or prevent an opportunistic herpes simplex virus type I and/or type II infection. In another specific embodiment, Therapeutics of the invention are used in any combination with PYRIMETHAMINE™ and/or LEUCOVORIN™ to prophylactically treat or prevent an

15 opportunistic *Toxoplasma gondii* infection. In another specific embodiment, Therapeutics of the invention are used in any combination with LEUCOVORIN™ and/or NEUPOGEN™ to prophylactically treat or prevent an opportunistic bacterial infection.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antiviral agent. Antiviral agents that may be administered with the

20 Therapeutics of the invention include, but are not limited to, acyclovir, ribavirin, amantadine, and remantidine.

In a further embodiment, the Therapeutics of the invention are administered in combination with an antibiotic agent. Antibiotic agents that may be administered with the Therapeutics of the invention include, but are not limited to, amoxicillin, beta-lactamases,

25 aminoglycosides, beta-lactam (glycopeptide), beta-lactamases, Clindamycin, chloramphenicol, cephalosporins, ciprofloxacin, ciprofloxacin, erythromycin, fluoroquinolones, macrolides, metronidazole, penicillins, quinolones, rifampin, streptomycin, sulfonamide, tetracyclines, trimethoprim, trimethoprim-sulfamthoxazole, and vancomycin.

Conventional nonspecific immunosuppressive agents, that may be administered in

30 combination with the Therapeutics of the invention include, but are not limited to, steroids, cyclosporine, cyclosporine analogs, cyclophosphamide methylprednisone, prednisone,

azathioprine, FK-506, 15-deoxyspergualin, and other immunosuppressive agents that act by suppressing the function of responding T cells.

In specific embodiments, Therapeutics of the invention are administered in combination with immunosuppressants. Immunosuppressants preparations that may be administered with the Therapeutics of the invention include, but are not limited to, ORTHOCLONE™ (OKT3), SANDIMMUNE™/NEORAL™/SANGDYA™ (cyclosporin), PROGRAF™ (tacrolimus), CELLCEPT™ (mycophenolate), Azathioprine, glucocorticosteroids, and RAPAMUNE™ (sirolimus). In a specific embodiment, immunosuppressants may be used to prevent rejection of organ or bone marrow transplantation.

In an additional embodiment, Therapeutics of the invention are administered alone or in combination with one or more intravenous immune globulin preparations. Intravenous immune globulin preparations that may be administered with the Therapeutics of the invention include, but not limited to, GAMMAR™, IVEEGAM™, SANDOGLOBULIN™, GAMMAGARD S/D™, and GAMIMUNE™. In a specific embodiment, Therapeutics of the invention are administered in combination with intravenous immune globulin preparations in transplantation therapy (e.g., bone marrow transplant).

In an additional embodiment, the Therapeutics of the invention are administered alone or in combination with an anti-inflammatory agent. Anti-inflammatory agents that may be administered with the Therapeutics of the invention include, but are not limited to, glucocorticoids and the nonsteroidal anti-inflammatories, aminoarylcarboxylic acid derivatives, arylacetic acid derivatives, arylbutyric acid derivatives, arylcarboxylic acids, arylpropionic acid derivatives, pyrazoles, pyrazolones, salicylic acid derivatives, thiazinecarboxamides, e-acetamidocaproic acid, S-adenosylmethionine, 3-amino-4-hydroxybutyric acid, amixetrine, bendazac, benzydamine, bucolome, difenpiramide, ditazol, emorfazone, guaiazulene, nabumetone, nimesulide, orgotein, oxaceprol, paranyline, perisoxal, pifoxime, proquazone, proxazole, and tenidap.

In another embodiment, compositions of the invention are administered in combination with a chemotherapeutic agent. Chemotherapeutic agents that may be administered with the Therapeutics of the invention include, but are not limited to, antibiotic derivatives (e.g., doxorubicin, bleomycin, daunorubicin, and dactinomycin); antiestrogens (e.g., tamoxifen); antimetabolites (e.g., fluorouracil, 5-FU, methotrexate, floxuridine, interferon alpha-2b, glutamic acid, plicamycin, mercaptopurine, and 6-thioguanine);

cytotoxic agents (e.g., carmustine, BCNU, lomustine, CCNU, cytosine arabinoside, cyclophosphamide, estramustine, hydroxyurea, procarbazine, mitomycin, busulfan, cis-platin, and vincristine sulfate); hormones (e.g., medroxyprogesterone, estramustine phosphate sodium, ethinyl estradiol, estradiol, megestrol acetate, methyltestosterone, diethylstilbestrol
5 diphosphate, chlorotrianisene, and testolactone); nitrogen mustard derivatives (e.g., mephallen, chorambucil, mechlorethamine (nitrogen mustard) and thiotepa); steroids and combinations (e.g., bethamethasone sodium phosphate); and others (e.g., dicarbazine, asparaginase, mitotane, vincristine sulfate, vinblastine sulfate, and etoposide).

In a specific embodiment, Therapeutics of the invention are administered in
10 combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or any combination of the components of CHOP. In another embodiment, Therapeutics of the invention are administered in combination with Rituximab. In a further embodiment, Therapeutics of the invention are administered with Rituxmab and CHOP, or Rituxmab and any combination of the components of CHOP.

15 In an additional embodiment, the Therapeutics of the invention are administered in combination with cytokines. Cytokines that may be administered with the Therapeutics of the invention include, but are not limited to, IL2, IL3, IL4, IL5, IL6, IL7, IL10, IL12, IL13, IL15, anti-CD40, CD40L, IFN-gamma and TNF-alpha. In another embodiment, Therapeutics of the invention may be administered with any interleukin, including, but not
20 limited to, IL-1alpha, IL-1beta, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, and IL-21.

In an additional embodiment, the Therapeutics of the invention are administered in combination with angiogenic proteins. Angiogenic proteins that may be administered with the Therapeutics of the invention include, but are not limited to, Glioma Derived Growth
25 Factor (GDGF), as disclosed in European Patent Number EP-399816; Platelet Derived Growth Factor-A (PDGF-A), as disclosed in European Patent Number EP-682110; Platelet Derived Growth Factor-B (PDGF-B), as disclosed in European Patent Number EP-282317; Placental Growth Factor (PIGF), as disclosed in International Publication Number WO 92/06194; Placental Growth Factor-2 (PIGF-2), as disclosed in Hauser et al., Growth Factors,
30 4:259-268 (1993); Vascular Endothelial Growth Factor (VEGF), as disclosed in International Publication Number WO 90/13649; Vascular Endothelial Growth Factor-A (VEGF-A), as disclosed in European Patent Number EP-506477; Vascular Endothelial Growth Factor-2

(VEGF-2), as disclosed in International Publication Number WO 96/39515; Vascular Endothelial Growth Factor B (VEGF-3); Vascular Endothelial Growth Factor B-186 (VEGF-B186), as disclosed in International Publication Number WO 96/26736; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO
5 98/02543; Vascular Endothelial Growth Factor-D (VEGF-D), as disclosed in International Publication Number WO 98/07832; and Vascular Endothelial Growth Factor-E (VEGF-E), as disclosed in German Patent Number DE19639601. The above mentioned references are incorporated herein by reference herein.

In an additional embodiment, the Therapeutics of the invention are administered in
10 combination with hematopoietic growth factors. Hematopoietic growth factors that may be administered with the Therapeutics of the invention include, but are not limited to, LEUKINE™ (SARGRAMOSTIM™) and NEUPOGEN™ (FILGRASTIM™).

In an additional embodiment, the Therapeutics of the invention are administered in combination with Fibroblast Growth Factors. Fibroblast Growth Factors that may be
15 administered with the Therapeutics of the invention include, but are not limited to, FGF-1, FGF-2, FGF-3, FGF-4, FGF-5, FGF-6, FGF-7, FGF-8, FGF-9, FGF-10, FGF-11, FGF-12, FGF-13, FGF-14, and FGF-15.

In additional embodiments, the Therapeutics of the invention are administered in combination with other therapeutic or prophylactic regimens, such as, for example, radiation
20 therapy.

Example 14: Method of Treating Decreased Levels of the Polypeptide

The present invention relates to a method for treating an individual in need of an
25 increased level of a polypeptide of the invention in the body comprising administering to such an individual a composition comprising a therapeutically effective amount of an agonist of the invention (including polypeptides of the invention). Moreover, it will be appreciated that conditions caused by a decrease in the standard or normal expression level of a polypeptide of the present invention in an individual can be treated by administering the
30 agonist or antagonist of the present invention. Thus, the invention also provides a method of treatment of an individual in need of an increased level of the polypeptide comprising administering to such an individual a Therapeutic comprising an amount of the agonist or

antagonist to increase the activity level of the polypeptide in such an individual.

For example, a patient with decreased levels of a polypeptide receives a daily dose 0.1-100 ug/kg of the agonist or antagonist for six consecutive days. The exact details of the dosing scheme, based on administration and formulation, are provided in Example 13.

5

Example 15: Method of Treating Increased Levels of the Polypeptide

The present invention also relates to a method of treating an individual in need of a decreased level of a polypeptide of the invention in the body comprising administering to
10 such an individual a composition comprising a therapeutically effective amount of an antagonist of the invention (including polypeptides and antibodies of the invention).

In one example, antisense technology is used to inhibit production of a polypeptide of the present invention. This technology is one example of a method of decreasing levels of a polypeptide, due to a variety of etiologies, such as cancer.

15 For example, a patient diagnosed with abnormally increased levels of a polypeptide is administered intravenously antisense polynucleotides at 0.5, 1.0, 1.5, 2.0 and 3.0 mg/kg day for 21 days. This treatment is repeated after a 7-day rest period if the treatment was well tolerated. The formulation of the antisense polynucleotide is provided in Example 13.

20 *Example 16: Method of Treatment Using Gene Therapy-Ex Vivo*

One method of gene therapy transplants fibroblasts, which are capable of expressing a polypeptide, onto a patient. Generally, fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in tissue-culture medium and separated into small pieces.
25 Small chunks of the tissue are placed on a wet surface of a tissue culture flask, approximately ten pieces are placed in each flask. The flask is turned upside down, closed tight and left at room temperature over night. After 24 hours at room temperature, the flask is inverted and the chunks of tissue remain fixed to the bottom of the flask and fresh media (e.g., Ham's F12 media, with 10% FBS, penicillin and streptomycin) is added. The flasks are then incubated
30 at 37 degree C for approximately one week.

At this time, fresh media is added and subsequently changed every several days. After an additional two weeks in culture, a monolayer of fibroblasts emerge. The monolayer

is trypsinized and scaled into larger flasks.

pMV-7 (Kirschmeier, P.T. et al., DNA, 7:219-25 (1988)), flanked by the long terminal repeats of the Moloney murine sarcoma virus, is digested with EcoRI and HindIII and subsequently treated with calf intestinal phosphatase. The linear vector is fractionated on
5 agarose gel and purified, using glass beads.

The cDNA encoding a polypeptide of the present invention can be amplified using PCR primers which correspond to the 5' and 3' end sequences respectively as set forth in Example 1 using primers and having appropriate restriction sites and initiation/stop codons, if
10 necessary. Preferably, the 5' primer contains an EcoRI site and the 3' primer includes a HindIII site. Equal quantities of the Moloney murine sarcoma virus linear backbone and the amplified EcoRI and HindIII fragment are added together, in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The ligation mixture is then used to transform bacteria HB101, which are then
15 plated onto agar containing kanamycin for the purpose of confirming that the vector has the gene of interest properly inserted.

The amphotropic pA317 or GP+am12 packaging cells are grown in tissue culture to confluent density in Dulbecco's Modified Eagles Medium (DMEM) with 10% calf serum (CS), penicillin and streptomycin. The MSV vector containing the gene is then added to the media and the packaging cells transduced with the vector. The packaging cells now produce
20 infectious viral particles containing the gene (the packaging cells are now referred to as producer cells).

Fresh media is added to the transduced producer cells, and subsequently, the media is harvested from a 10 cm plate of confluent producer cells. The spent media, containing the infectious viral particles, is filtered through a millipore filter to remove detached producer
25 cells and this media is then used to infect fibroblast cells. Media is removed from a sub-confluent plate of fibroblasts and quickly replaced with the media from the producer cells. This media is removed and replaced with fresh media. If the titer of virus is high, then virtually all fibroblasts will be infected and no selection is required. If the titer is very low, then it is necessary to use a retroviral vector that has a selectable marker, such as neo or his.
30 Once the fibroblasts have been efficiently infected, the fibroblasts are analyzed to determine whether protein is produced.

The engineered fibroblasts are then transplanted onto the host, either alone or after

having been grown to confluence on cytodex 3 microcarrier beads.

Example 17: Gene Therapy Using Endogenous Genes Corresponding To Polynucleotides of the Invention

5

Another method of gene therapy according to the present invention involves operably associating the endogenous polynucleotide sequence of the invention with a promoter via homologous recombination as described, for example, in U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; 10 International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., *Proc. Natl. Acad. Sci. USA*, 86:8932-8935 (1989); and Zijlstra et al., *Nature*, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not expressed in the cells, or is expressed at a lower level than desired.

Polynucleotide constructs are made which contain a promoter and targeting 15 sequences, which are homologous to the 5' non-coding sequence of endogenous polynucleotide sequence, flanking the promoter. The targeting sequence will be sufficiently near the 5' end of the polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination. The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct 20 restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter.

The amplified promoter and the amplified targeting sequences are digested with the 25 appropriate restriction enzymes and subsequently treated with calf intestinal phosphatase. The digested promoter and digested targeting sequences are added together in the presence of T4 DNA ligase. The resulting mixture is maintained under conditions appropriate for ligation of the two fragments. The construct is size fractionated on an agarose gel then purified by phenol extraction and ethanol precipitation.

30 In this Example, the polynucleotide constructs are administered as naked polynucleotides via electroporation. However, the polynucleotide constructs may also be administered with transfection-facilitating agents, such as liposomes, viral sequences, viral

particles, precipitating agents, etc. Such methods of delivery are known in the art.

Once the cells are transfected, homologous recombination will take place which results in the promoter being operably linked to the endogenous polynucleotide sequence. This results in the expression of polynucleotide corresponding to the polynucleotide in the cell. Expression may be detected by immunological staining, or any other method known in the art.

Fibroblasts are obtained from a subject by skin biopsy. The resulting tissue is placed in DMEM + 10% fetal calf serum. Exponentially growing or early stationary phase fibroblasts are trypsinized and rinsed from the plastic surface with nutrient medium. An aliquot of the cell suspension is removed for counting, and the remaining cells are subjected to centrifugation. The supernatant is aspirated and the pellet is resuspended in 5 ml of electroporation buffer (20 mM HEPES pH 7.3, 137 mM NaCl, 5 mM KCl, 0.7 mM Na₂HPO₄, 6 mM dextrose). The cells are recentrifuged, the supernatant aspirated, and the cells resuspended in electroporation buffer containing 1 mg/ml acetylated bovine serum albumin. The final cell suspension contains approximately 3×10^6 cells/ml. Electroporation should be performed immediately following resuspension.

Plasmid DNA is prepared according to standard techniques. For example, to construct a plasmid for targeting to the locus corresponding to the polynucleotide of the invention, plasmid pUC18 (MBI Fermentas, Amherst, NY) is digested with HindIII. The CMV promoter is amplified by PCR with an XbaI site on the 5' end and a BamHI site on the 3' end. Two non-coding sequences are amplified via PCR: one non-coding sequence (fragment 1) is amplified with a HindIII site at the 5' end and an Xba site at the 3' end; the other non-coding sequence (fragment 2) is amplified with a BamHI site at the 5' end and a HindIII site at the 3' end. The CMV promoter and the fragments (1 and 2) are digested with the appropriate enzymes (CMV promoter - XbaI and BamHI; fragment 1 - XbaI; fragment 2 - BamHI) and ligated together. The resulting ligation product is digested with HindIII, and ligated with the HindIII-digested pUC18 plasmid.

Plasmid DNA is added to a sterile cuvette with a 0.4 cm electrode gap (Bio-Rad). The final DNA concentration is generally at least 120 µg/ml. 0.5 ml of the cell suspension (containing approximately 1.5×10^6 cells) is then added to the cuvette, and the cell suspension and DNA solutions are gently mixed. Electroporation is performed with a Gene-Pulser apparatus (Bio-Rad). Capacitance and voltage are set at 960 µF and 250-300 V,

respectively. As voltage increases, cell survival decreases, but the percentage of surviving cells that stably incorporate the introduced DNA into their genome increases dramatically. Given these parameters, a pulse time of approximately 14-20 mSec should be observed.

Electroporated cells are maintained at room temperature for approximately 5 min, and the contents of the cuvette are then gently removed with a sterile transfer pipette. The cells are added directly to 10 ml of prewarmed nutrient media (DMEM with 15% calf serum) in a 10 cm dish and incubated at 37 degree C. The following day, the media is aspirated and replaced with 10 ml of fresh media and incubated for a further 16-24 hours.

The engineered fibroblasts are then injected into the host, either alone or after having been grown to confluence on cytodex 3 microcarrier beads. The fibroblasts now produce the protein product. The fibroblasts can then be introduced into a patient as described above.

Example 18: Method of Treatment Using Gene Therapy - In Vivo

Another aspect of the present invention is using *in vivo* gene therapy methods to treat disorders, diseases and conditions. The gene therapy method relates to the introduction of naked nucleic acid (DNA, RNA, and antisense DNA or RNA) sequences into an animal to increase or decrease the expression of the polypeptide. The polynucleotide of the present invention may be operatively linked to a promoter or any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques and methods are known in the art, see, for example, WO90/11092, WO98/11779; U.S. Patent NO. 5693622, 5705151, 5580859; Tabata et al., Cardiovasc. Res. 35(3):470-479 (1997); Chao et al., Pharmacol. Res. 35(6):517-522 (1997); Wolff, Neuromuscul. Disord. 7(5):314-318 (1997); Schwartz et al., Gene Ther. 3(5):405-411 (1996); Tsurumi et al., Circulation 94(12):3281-3290 (1996) (incorporated herein by reference).

The polynucleotide constructs may be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, intestine and the like). The polynucleotide constructs can be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

The term "naked" polynucleotide, DNA or RNA, refers to sequences that are free from any delivery vehicle that acts to assist, promote, or facilitate entry into the cell,

including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the present invention may also be delivered in liposome formulations (such as those taught in Felgner P.L. et al. (1995) Ann. NY Acad. Sci. 772:126-139 and Abdallah B. et al. (1995) Biol. Cell 85(1):1-7) which can be prepared by methods well known to those skilled in the art.

The polynucleotide vector constructs used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Any strong promoter known to those skilled in the art can be used for driving the expression of DNA. Unlike other gene therapies techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

The polynucleotide construct can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

For the naked polynucleotide injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 g/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will

appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration. The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked polynucleotide constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

The dose response effects of injected polynucleotide in muscle *in vivo* is determined as follows. Suitable template DNA for production of mRNA coding for polypeptide of the present invention is prepared in accordance with a standard recombinant DNA methodology. The template DNA, which may be either circular or linear, is either used as naked DNA or complexed with liposomes. The quadriceps muscles of mice are then injected with various amounts of the template DNA.

Five to six week old female and male Balb/C mice are anesthetized by intraperitoneal injection with 0.3 ml of 2.5% Avertin. A 1.5 cm incision is made on the anterior thigh, and the quadriceps muscle is directly visualized. The template DNA is injected in 0.1 ml of carrier in a 1 cc syringe through a 27 gauge needle over one minute, approximately 0.5 cm from the distal insertion site of the muscle into the knee and about 0.2 cm deep. A suture is placed over the injection site for future localization, and the skin is closed with stainless steel clips.

After an appropriate incubation time (e.g., 7 days) muscle extracts are prepared by excising the entire quadriceps. Every fifth 15 um cross-section of the individual quadriceps muscles is histochemically stained for protein expression. A time course for protein expression may be done in a similar fashion except that quadriceps from different mice are harvested at different times. Persistence of DNA in muscle following injection may be determined by Southern blot analysis after preparing total cellular DNA and HIRT supernatants from injected and control mice. The results of the above experimentation in mice can be use to extrapolate proper dosages and other treatment parameters in humans and other animals using naked DNA.

Example 19: Transgenic Animals

The polypeptides of the invention can also be expressed in transgenic animals. Animals of any species, including, but not limited to, mice, rats, rabbits, hamsters, guinea pigs, pigs, micro-pigs, goats, sheep, cows and non-human primates, *e.g.*, baboons, monkeys, and chimpanzees may be used to generate transgenic animals. In a specific embodiment, techniques described herein or otherwise known in the art, are used to express polypeptides of the invention in humans, as part of a gene therapy protocol.

Any technique known in the art may be used to introduce the transgene (*i.e.*, polynucleotides of the invention) into animals to produce the founder lines of transgenic animals. Such techniques include, but are not limited to, pronuclear microinjection (Paterson et al., Appl. Microbiol. Biotechnol. 40:691-698 (1994); Carver et al., Biotechnology (NY) 11:1263-1270 (1993); Wright et al., Biotechnology (NY) 9:830-834 (1991); and Hoppe et al., U.S. Pat. No. 4,873,191 (1989)); retrovirus mediated gene transfer into germ lines (Van der Putten et al., Proc. Natl. Acad. Sci., USA 82:6148-6152 (1985)), blastocysts or embryos; gene targeting in embryonic stem cells (Thompson et al., Cell 56:313-321 (1989)); electroporation of cells or embryos (Lo, 1983, Mol Cell. Biol. 3:1803-1814 (1983)); introduction of the polynucleotides of the invention using a gene gun (see, *e.g.*, Ulmer et al., Science 259:1745 (1993); introducing nucleic acid constructs into embryonic pluripotent stem cells and transferring the stem cells back into the blastocyst; and sperm-mediated gene transfer (Lavitrano et al., Cell 57:717-723 (1989); etc. For a review of such techniques, see Gordon, "Transgenic Animals," Intl. Rev. Cytol. 115:171-229 (1989), which is incorporated by reference herein in its entirety.

Any technique known in the art may be used to produce transgenic clones containing polynucleotides of the invention, for example, nuclear transfer into enucleated oocytes of nuclei from cultured embryonic, fetal, or adult cells induced to quiescence (Campbell et al., Nature 380:64-66 (1996); Wilmut et al., Nature 385:810-813 (1997)).

The present invention provides for transgenic animals that carry the transgene in all their cells, as well as animals which carry the transgene in some, but not all their cells, *i.e.*, mosaic animals or chimeric. The transgene may be integrated as a single transgene or as multiple copies such as in concatamers, *e.g.*, head-to-head tandems or head-to-tail tandems. The transgene may also be selectively introduced into and activated in a particular cell type by following, for example, the teaching of Lasko et al. (Lasko et al., Proc. Natl. Acad. Sci.

USA 89:6232-6236 (1992)). The regulatory sequences required for such a cell-type specific activation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art. When it is desired that the polynucleotide transgene be integrated into the chromosomal site of the endogenous gene, gene targeting is preferred. Briefly, when such a technique is to be utilized, vectors containing some nucleotide sequences homologous to the endogenous gene are designed for the purpose of integrating, via homologous recombination with chromosomal sequences, into and disrupting the function of the nucleotide sequence of the endogenous gene. The transgene may also be selectively introduced into a particular cell type, thus inactivating the endogenous gene in only that cell type, by following, for example, the teaching of Gu et al. (Gu et al., Science 265:103-106 (1994)). The regulatory sequences required for such a cell-type specific inactivation will depend upon the particular cell type of interest, and will be apparent to those of skill in the art.

Once transgenic animals have been generated, the expression of the recombinant gene may be assayed utilizing standard techniques. Initial screening may be accomplished by Southern blot analysis or PCR techniques to analyze animal tissues to verify that integration of the transgene has taken place. The level of mRNA expression of the transgene in the tissues of the transgenic animals may also be assessed using techniques which include, but are not limited to, Northern blot analysis of tissue samples obtained from the animal, *in situ* hybridization analysis, and reverse transcriptase-PCR (rt-PCR). Samples of transgenic gene-expressing tissue may also be evaluated immunocytochemically or immunohistochemically using antibodies specific for the transgene product.

Once the founder animals are produced, they may be bred, inbred, outbred, or crossbred to produce colonies of the particular animal. Examples of such breeding strategies include, but are not limited to: outbreeding of founder animals with more than one integration site in order to establish separate lines; inbreeding of separate lines in order to produce compound transgenics that express the transgene at higher levels because of the effects of additive expression of each transgene; crossing of heterozygous transgenic animals to produce animals homozygous for a given integration site in order to both augment expression and eliminate the need for screening of animals by DNA analysis; crossing of separate homozygous lines to produce compound heterozygous or homozygous lines; and breeding to place the transgene on a distinct background that is appropriate for an experimental model of interest.

Transgenic animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

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Example 20: Knock-Out Animals

Endogenous gene expression can also be reduced by inactivating or "knocking out" the gene and/or its promoter using targeted homologous recombination. (*E.g.*, see Smithies et al., *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson et al., *Cell* 5:313-321 (1989); each of which is incorporated by reference herein in its entirety). For example, a mutant, non-functional polynucleotide of the invention (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous polynucleotide sequence (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express polypeptides of the invention *in vivo*. In another embodiment, techniques known in the art are used to generate knockouts in cells that contain, but do not express the gene of interest. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the targeted gene. Such approaches are particularly suited in research and agricultural fields where modifications to embryonic stem cells can be used to generate animal offspring with an inactive targeted gene (*e.g.*, see Thomas & Capecchi 1987 and Thompson 1989, *supra*). However this approach can be routinely adapted for use in humans provided the recombinant DNA constructs are directly administered or targeted to the required site *in vivo* using appropriate viral vectors that will be apparent to those of skill in the art.

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In further embodiments of the invention, cells that are genetically engineered to express the polypeptides of the invention, or alternatively, that are genetically engineered not to express the polypeptides of the invention (*e.g.*, knockouts) are administered to a patient *in vivo*. Such cells may be obtained from the patient (*i.e.*, animal, including human) or an MHC compatible donor and can include, but are not limited to fibroblasts, bone marrow cells, blood cells (*e.g.*, lymphocytes), adipocytes, muscle cells, endothelial cells etc. The cells are genetically engineered *in vitro* using recombinant DNA techniques to introduce the coding

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sequence of polypeptides of the invention into the cells, or alternatively, to disrupt the coding sequence and/or endogenous regulatory sequence associated with the polypeptides of the invention, e.g., by transduction (using viral vectors, and preferably vectors that integrate the transgene into the cell genome) or transfection procedures, including, but not limited to, the use of plasmids, cosmids, YACs, naked DNA, electroporation, liposomes, etc. The coding sequence of the polypeptides of the invention can be placed under the control of a strong constitutive or inducible promoter or promoter/enhancer to achieve expression, and preferably secretion, of the polypeptides of the invention. The engineered cells which express and preferably secrete the polypeptides of the invention can be introduced into the patient systemically, e.g., in the circulation, or intraperitoneally.

Alternatively, the cells can be incorporated into a matrix and implanted in the body, e.g., genetically engineered fibroblasts can be implanted as part of a skin graft; genetically engineered endothelial cells can be implanted as part of a lymphatic or vascular graft. (See, for example, Anderson et al. U.S. Patent No. 5,399,349; and Mulligan & Wilson, U.S. Patent No. 5,460,959 each of which is incorporated by reference herein in its entirety).

When the cells to be administered are non-autologous or non-MHC compatible cells, they can be administered using well known techniques which prevent the development of a host immune response against the introduced cells. For example, the cells may be introduced in an encapsulated form which, while allowing for an exchange of components with the immediate extracellular environment, does not allow the introduced cells to be recognized by the host immune system.

Transgenic and "knock-out" animals of the invention have uses which include, but are not limited to, animal model systems useful in elaborating the biological function of polypeptides of the present invention, studying conditions and/or disorders associated with aberrant expression, and in screening for compounds effective in ameliorating such conditions and/or disorders.

Example 22: Assays Detecting Stimulation or Inhibition of B cell Proliferation and Differentiation

Generation of functional humoral immune responses requires both soluble and cognate signaling between B-lineage cells and their microenvironment. Signals may impart a

positive stimulus that allows a B-lineage cell to continue its programmed development, or a negative stimulus that instructs the cell to arrest its current developmental pathway. To date, numerous stimulatory and inhibitory signals have been found to influence B cell responsiveness including IL-2, IL-4, IL-5, IL-6, IL-7, IL10, IL-13, IL-14 and IL-15.

5 Interestingly, these signals are by themselves weak effectors but can, in combination with various co-stimulatory proteins, induce activation, proliferation, differentiation, homing, tolerance and death among B cell populations.

One of the best studied classes of B-cell co-stimulatory proteins is the TNF-superfamily. Within this family CD40, CD27, and CD30 along with their respective ligands
10 CD154, CD70, and CD153 have been found to regulate a variety of immune responses. Assays which allow for the detection and/or observation of the proliferation and differentiation of these B-cell populations and their precursors are valuable tools in determining the effects various proteins may have on these B-cell populations in terms of proliferation and differentiation. Listed below are two assays designed to allow for the
15 detection of the differentiation, proliferation, or inhibition of B-cell populations and their precursors.

In Vitro Assay- Agonists or antagonists of the invention can be assessed for its ability to induce activation, proliferation, differentiation or inhibition and/or death in B-cell populations and their precursors. The activity of the agonists or antagonists of the invention
20 on purified human tonsillar B cells, measured qualitatively over the dose range from 0.1 to 10,000 ng/mL, is assessed in a standard B-lymphocyte co-stimulation assay in which purified tonsillar B cells are cultured in the presence of either formalin-fixed *Staphylococcus aureus* Cowan I (SAC) or immobilized anti-human IgM antibody as the priming agent. Second signals such as IL-2 and IL-15 synergize with SAC and IgM crosslinking to elicit B cell
25 proliferation as measured by tritiated-thymidine incorporation. Novel synergizing agents can be readily identified using this assay. The assay involves isolating human tonsillar B cells by magnetic bead (MACS) depletion of CD3-positive cells. The resulting cell population is greater than 95% B cells as assessed by expression of CD45R(B220).

Various dilutions of each sample are placed into individual wells of a 96-well plate to
30 which are added 10^5 B-cells suspended in culture medium (RPMI 1640 containing 10% FBS, 5×10^{-5} M 2ME, 100U/ml penicillin, 10ug/ml streptomycin, and 10^{-5} dilution of SAC) in a total volume of 150ul. Proliferation or inhibition is quantitated by a 20h pulse (1uCi/well)

with 3H-thymidine (6.7 Ci/mM) beginning 72h post factor addition. The positive and negative controls are IL2 and medium respectively.

In Vivo Assay- BALB/c mice are injected (i.p.) twice per day with buffer only, or 2 mg/Kg of agonists or antagonists of the invention, or truncated forms thereof. Mice receive this treatment for 4 consecutive days, at which time they are sacrificed and various tissues and serum collected for analyses. Comparison of H&E sections from normal spleens and spleens treated with agonists or antagonists of the invention identify the results of the activity of the agonists or antagonists on spleen cells, such as the diffusion of peri-arterial lymphatic sheaths, and/or significant increases in the nucleated cellularity of the red pulp regions, which may indicate the activation of the differentiation and proliferation of B-cell populations. Immunohistochemical studies using a B cell marker, anti-CD45R(B220), are used to determine whether any physiological changes to splenic cells, such as splenic disorganization, are due to increased B-cell representation within loosely defined B-cell zones that infiltrate established T-cell regions.

Flow cytometric analyses of the spleens from mice treated with agonist or antagonist is used to indicate whether the agonists or antagonists specifically increases the proportion of ThB+, CD45R(B220)dull B cells over that which is observed in control mice.

Likewise, a predicted consequence of increased mature B-cell representation in vivo is a relative increase in serum Ig titers. Accordingly, serum IgM and IgA levels are compared between buffer and agonists or antagonists-treated mice.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 23: T Cell Proliferation Assay

A CD3-induced proliferation assay is performed on PBMCs and is measured by the uptake of ³H-thymidine. The assay is performed as follows. Ninety-six well plates are coated with 100 µl/well of mAb to CD3 (HIT3a, Pharmingen) or isotype-matched control mAb (B33.1) overnight at 4 degrees C (1 µg/ml in .05M bicarbonate buffer, pH 9.5), then washed three times with PBS. PBMC are isolated by F/H gradient centrifugation from human peripheral blood and added to quadruplicate wells (5 x 10⁴/well) of mAb coated plates

in RPMI containing 10% FCS and P/S in the presence of varying concentrations of agonists or antagonists of the invention (total volume 200 μ l). Relevant protein buffer and medium alone are controls. After 48 hr. culture at 37 degrees C, plates are spun for 2 min. at 1000 rpm and 100 μ l of supernatant is removed and stored -20 degrees C for measurement of IL-2 (or other cytokines) if effect on proliferation is observed. Wells are supplemented with 100 μ l of medium containing 0.5 μ Ci of 3 H-thymidine and cultured at 37 degrees C for 18-24 hr. Wells are harvested and incorporation of 3 H-thymidine used as a measure of proliferation. Anti-CD3 alone is the positive control for proliferation. IL-2 (100 U/ml) is also used as a control which enhances proliferation. Control antibody which does not induce proliferation of T cells is used as the negative controls for the effects of agonists or antagonists of the invention.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 24: Effect of Agonists or Antagonists of the Invention on the Expression of MHC Class II, Costimulatory and Adhesion Molecules and Cell Differentiation of Monocytes and Monocyte-Derived Human Dendritic Cells

Dendritic cells are generated by the expansion of proliferating precursors found in the peripheral blood: adherent PBMC or elutriated monocytic fractions are cultured for 7-10 days with GM-CSF (50 ng/ml) and IL-4 (20 ng/ml). These dendritic cells have the characteristic phenotype of immature cells (expression of CD1, CD80, CD86, CD40 and MHC class II antigens). Treatment with activating factors, such as TNF- α , causes a rapid change in surface phenotype (increased expression of MHC class I and II, costimulatory and adhesion molecules, downregulation of FC γ RII, upregulation of CD83). These changes correlate with increased antigen-presenting capacity and with functional maturation of the dendritic cells.

FACS analysis of surface antigens is performed as follows. Cells are treated 1-3 days with increasing concentrations of agonist or antagonist of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degrees C. After an additional wash, the labeled cells are analyzed by flow

cytometry on a FACScan (Becton Dickinson).

Effect on the production of cytokines. Cytokines generated by dendritic cells, in particular IL-12, are important in the initiation of T-cell dependent immune responses. IL-12 strongly influences the development of Th1 helper T-cell immune response, and induces cytotoxic T and NK cell function. An ELISA is used to measure the IL-12 release as follows. Dendritic cells (10^6 /ml) are treated with increasing concentrations of agonists or antagonists of the invention for 24 hours. LPS (100 ng/ml) is added to the cell culture as positive control. Supernatants from the cell cultures are then collected and analyzed for IL-12 content using commercial ELISA kit (e.g., R & D Systems (Minneapolis, MN)). The standard protocols provided with the kits are used.

Effect on the expression of MHC Class II, costimulatory and adhesion molecules. Three major families of cell surface antigens can be identified on monocytes: adhesion molecules, molecules involved in antigen presentation, and Fc receptor. Modulation of the expression of MHC class II antigens and other costimulatory molecules, such as B7 and ICAM-1, may result in changes in the antigen presenting capacity of monocytes and ability to induce T cell activation. Increase expression of Fc receptors may correlate with improved monocyte cytotoxic activity, cytokine release and phagocytosis.

FACS analysis is used to examine the surface antigens as follows. Monocytes are treated 1-5 days with increasing concentrations of agonists or antagonists of the invention or LPS (positive control), washed with PBS containing 1% BSA and 0.02 mM sodium azide, and then incubated with 1:20 dilution of appropriate FITC- or PE-labeled monoclonal antibodies for 30 minutes at 4 degreesC. After an additional wash, the labeled cells are analyzed by flow cytometry on a FACScan (Becton Dickinson).

Monocyte activation and/or increased survival. Assays for molecules that activate (or alternatively, inactivate) monocytes and/or increase monocyte survival (or alternatively, decrease monocyte survival) are known in the art and may routinely be applied to determine whether a molecule of the invention functions as an inhibitor or activator of monocytes. Agonists or antagonists of the invention can be screened using the three assays described below. For each of these assays, Peripheral blood mononuclear cells (PBMC) are purified

from single donor leukopacks (American Red Cross, Baltimore, MD) by centrifugation through a Histopaque gradient (Sigma). Monocytes are isolated from PBMC by counterflow centrifugal elutriation.

- 5 Monocyte Survival Assay. Human peripheral blood monocytes progressively lose viability when cultured in absence of serum or other stimuli. Their death results from internally regulated process (apoptosis). Addition to the culture of activating factors, such as TNF-alpha dramatically improves cell survival and prevents DNA fragmentation. Propidium iodide (PI) staining is used to measure apoptosis as follows. Monocytes are cultured for 48 hours in
10 polypropylene tubes in serum-free medium (positive control), in the presence of 100 ng/ml TNF-alpha (negative control), and in the presence of varying concentrations of the compound to be tested. Cells are suspended at a concentration of 2×10^6 /ml in PBS containing PI at a final concentration of 5 μ g/ml, and then incubated at room temperature for 5 minutes before FACScan analysis. PI uptake has been demonstrated to correlate with DNA fragmentation in
15 this experimental paradigm.

- Effect on cytokine release. An important function of monocytes/macrophages is their regulatory activity on other cellular populations of the immune system through the release of cytokines after stimulation. An ELISA to measure cytokine release is performed as follows.
20 Human monocytes are incubated at a density of 5×10^5 cells/ml with increasing concentrations of agonists or antagonists of the invention and under the same conditions, but in the absence of agonists or antagonists. For IL-12 production, the cells are primed overnight with IFN (100 U/ml) in presence of agonist or antagonist of the invention. LPS (10 ng/ml) is then added. Conditioned media are collected after 24h and kept frozen until use.
25 Measurement of TNF-alpha, IL-10, MCP-1 and IL-8 is then performed using a commercially available ELISA kit (e. g, R & D Systems (Minneapolis, MN)) and applying the standard protocols provided with the kit.

- Oxidative burst. Purified monocytes are plated in 96-w plate at 2×10^5 cell/well. Increasing
30 concentrations of agonists or antagonists of the invention are added to the wells in a total volume of 0.2 ml culture medium (RPMI 1640 + 10% FCS, glutamine and antibiotics). After 3 days incubation, the plates are centrifuged and the medium is removed from the wells. To

the macrophage monolayers, 0.2 ml per well of phenol red solution (140 mM NaCl, 10 mM potassium phosphate buffer pH 7.0, 5.5 mM dextrose, 0.56 mM phenol red and 19 U/ml of HRPO) is added, together with the stimulant (200 nM PMA). The plates are incubated at 37°C for 2 hours and the reaction is stopped by adding 20 µl 1N NaOH per well. The
5 absorbance is read at 610 nm. To calculate the amount of H₂O₂ produced by the macrophages, a standard curve of a H₂O₂ solution of known molarity is performed for each experiment.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 25: Biological Effects of Agonists or Antagonists of the Invention

15 Astrocyte and Neuronal Assays.

Agonists or antagonists of the invention, expressed in *Escherichia coli* and purified as described above, can be tested for activity in promoting the survival, neurite outgrowth, or phenotypic differentiation of cortical neuronal cells and for inducing the proliferation of glial fibrillary acidic protein immunopositive cells, astrocytes. The selection of cortical cells for
20 the bioassay is based on the prevalent expression of FGF-1 and FGF-2 in cortical structures and on the previously reported enhancement of cortical neuronal survival resulting from FGF-2 treatment. A thymidine incorporation assay, for example, can be used to elucidate an agonist or antagonist of the invention's activity on these cells.

Moreover, previous reports describing the biological effects of FGF-2 (basic FGF) on
25 cortical or hippocampal neurons *in vitro* have demonstrated increases in both neuron survival and neurite outgrowth (Walicke et al., "Fibroblast growth factor promotes survival of dissociated hippocampal neurons and enhances neurite extension." *Proc. Natl. Acad. Sci. USA* 83:3012-3016. (1986), assay herein incorporated by reference in its entirety). However, reports from experiments done on PC-12 cells suggest that these two responses are not
30 necessarily synonymous and may depend on not only which FGF is being tested but also on which receptor(s) are expressed on the target cells. Using the primary cortical neuronal

culture paradigm, the ability of an agonist or antagonist of the invention to induce neurite outgrowth can be compared to the response achieved with FGF-2 using, for example, a thymidine incorporation assay.

5 Fibroblast and endothelial cell assays.

Human lung fibroblasts are obtained from Clonetics (San Diego, CA) and maintained in growth media from Clonetics. Dermal microvascular endothelial cells are obtained from Cell Applications (San Diego, CA). For proliferation assays, the human lung fibroblasts and dermal microvascular endothelial cells can be cultured at 5,000 cells/well in a 96-well plate
10 for one day in growth medium. The cells are then incubated for one day in 0.1% BSA basal medium. After replacing the medium with fresh 0.1% BSA medium, the cells are incubated with the test proteins for 3 days. Alamar Blue (Alamar Biosciences, Sacramento, CA) is added to each well to a final concentration of 10%. The cells are incubated for 4 hr. Cell viability is measured by reading in a CytoFluor fluorescence reader. For the PGE₂ assays,
15 the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or agonists or antagonists of the invention with or without IL-1 α for 24 hours. The supernatants are collected and assayed for PGE₂ by EIA kit (Cayman, Ann Arbor, MI). For the IL-6 assays, the human lung fibroblasts are cultured at 5,000 cells/well in a 96-well plate for one
20 day. After a medium change to 0.1% BSA basal medium, the cells are incubated with FGF-2 or with or without agonists or antagonists of the invention IL-1 α for 24 hours. The supernatants are collected and assayed for IL-6 by ELISA kit (Endogen, Cambridge, MA).

Human lung fibroblasts are cultured with FGF-2 or agonists or antagonists of the invention for 3 days in basal medium before the addition of Alamar Blue to assess effects on
25 growth of the fibroblasts. FGF-2 should show a stimulation at 10 - 2500 ng/ml which can be used to compare stimulation with agonists or antagonists of the invention.

Parkinson Models.

The loss of motor function in Parkinson's disease is attributed to a deficiency of
30 striatal dopamine resulting from the degeneration of the nigrostriatal dopaminergic projection

neurons. An animal model for Parkinson's that has been extensively characterized involves the systemic administration of 1-methyl-4 phenyl 1,2,3,6-tetrahydropyridine (MPTP). In the CNS, MPTP is taken-up by astrocytes and catabolized by monoamine oxidase B to 1-methyl-4-phenyl pyridine (MPP^+) and released. Subsequently, MPP^+ is actively accumulated in
5 dopaminergic neurons by the high-affinity reuptake transporter for dopamine. MPP^+ is then concentrated in mitochondria by the electrochemical gradient and selectively inhibits nicotinamide adenine disphosphate: ubiquinone oxidoreductionase (complex I), thereby interfering with electron transport and eventually generating oxygen radicals.

It has been demonstrated in tissue culture paradigms that FGF-2 (basic FGF) has
10 trophic activity towards nigral dopaminergic neurons (Ferrari et al., Dev. Biol. 1989). Recently, Dr. Unsicker's group has demonstrated that administering FGF-2 in gel foam implants in the striatum results in the near complete protection of nigral dopaminergic neurons from the toxicity associated with MPTP exposure (Otto and Unsicker, J. Neuroscience, 1990).

Based on the data with FGF-2, agonists or antagonists of the invention can be
15 evaluated to determine whether it has an action similar to that of FGF-2 in enhancing dopaminergic neuronal survival *in vitro* and it can also be tested *in vivo* for protection of dopaminergic neurons in the striatum from the damage associated with MPTP treatment. The potential effect of an agonist or antagonist of the invention is first examined *in vitro* in a
20 dopaminergic neuronal cell culture paradigm. The cultures are prepared by dissecting the midbrain floor plate from gestation day 14 Wistar rat embryos. The tissue is dissociated with trypsin and seeded at a density of 200,000 cells/cm² on polyorthinine-laminin coated glass coverslips. The cells are maintained in Dulbecco's Modified Eagle's medium and F12 medium containing hormonal supplements (N1). The cultures are fixed with
25 paraformaldehyde after 8 days *in vitro* and are processed for tyrosine hydroxylase, a specific marker for dopaminergic neurons, immunohistochemical staining. Dissociated cell cultures are prepared from embryonic rats. The culture medium is changed every third day and the factors are also added at that time.

Since the dopaminergic neurons are isolated from animals at gestation day 14, a
30 developmental time which is past the stage when the dopaminergic precursor cells are proliferating, an increase in the number of tyrosine hydroxylase immunopositive neurons would represent an increase in the number of dopaminergic neurons surviving *in vitro*.

Therefore, if an agonist or antagonist of the invention acts to prolong the survival of dopaminergic neurons, it would suggest that the agonist or antagonist may be involved in Parkinson's Disease.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 26: The Effect of Agonists or Antagonists of the Invention on the Growth of Vascular Endothelial Cells

On day 1, human umbilical vein endothelial cells (HUVEC) are seeded at 2.5×10^4 cells/35 mm dish density in M199 medium containing 4% fetal bovine serum (FBS), 16 units/ml heparin, and 50 units/ml endothelial cell growth supplements (ECGS, Biotechnology, Inc.). On day 2, the medium is replaced with M199 containing 10% FBS, 8 units/ml heparin. An agonist or antagonist of the invention, and positive controls, such as VEGF and basic FGF (bFGF) are added, at varying concentrations. On days 4 and 6, the medium is replaced. On day 8, cell number is determined with a Coulter Counter.

An increase in the number of HUVEC cells indicates that the compound of the invention may proliferate vascular endothelial cells, while a decrease in the number of HUVEC cell indicates that the compound of the invention inhibits vascular endothelial cells.

The studies described in this example tested activity of a polypeptide of the invention. However, one skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), agonists, and/or antagonists of the invention.

Example 27: Rat Corneal Wound Healing Model

This animal model shows the effect of an agonist or antagonist of the invention on neovascularization. The experimental protocol includes:

- a) Making a 1-1.5 mm long incision from the center of cornea into the stromal layer.
- b) Inserting a spatula below the lip of the incision facing the outer corner of the

eye.

c) Making a pocket (its base is 1-1.5 mm from the edge of the eye).

d) Positioning a pellet, containing 50ng- 5ug of an agonist or antagonist of the invention, within the pocket.

5 e) Treatment with an agonist or antagonist of the invention can also be applied topically to the corneal wounds in a dosage range of 20mg - 500mg (daily treatment for five days).

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 28: Diabetic Mouse and Glucocorticoid-Impaired Wound Healing Models

A. Diabetic db+/db+ Mouse Model.

15 To demonstrate that an agonist or antagonist of the invention accelerates the healing process, the genetically diabetic mouse model of wound healing is used. The full thickness wound healing model in the db+/db+ mouse is a well characterized, clinically relevant and reproducible model of impaired wound healing. Healing of the diabetic wound is dependent on formation of granulation tissue and re-epithelialization rather than contraction (Gartner,
20 M.H. *et al.*, *J. Surg. Res.* 52:389 (1992); Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)).

The diabetic animals have many of the characteristic features observed in Type II diabetes mellitus. Homozygous (db+/db+) mice are obese in comparison to their normal heterozygous (db+/+m) littermates. Mutant diabetic (db+/db+) mice have a single autosomal
25 recessive mutation on chromosome 4 (db+) (Coleman *et al.* *Proc. Natl. Acad. Sci. USA* 77:283-293 (1982)). Animals show polyphagia, polydipsia and polyuria. Mutant diabetic mice (db+/db+) have elevated blood glucose, increased or normal insulin levels, and suppressed cell-mediated immunity (Mandel *et al.*, *J. Immunol.* 120:1375 (1978); Debray-Sachs, M. *et al.*, *Clin. Exp. Immunol.* 51(1):1-7 (1983); Leiter *et al.*, *Am. J. of Pathol.* 114:46-
30 55 (1985)). Peripheral neuropathy, myocardial complications, and microvascular lesions, basement membrane thickening and glomerular filtration abnormalities have been described in these animals (Norido, F. *et al.*, *Exp. Neurol.* 83(2):221-232 (1984); Robertson *et al.*,

Diabetes 29(1):60-67 (1980); Giacomelli *et al.*, *Lab Invest.* 40(4):460-473 (1979); Coleman, D.L., *Diabetes* 31 (Suppl):1-6 (1982)). These homozygous diabetic mice develop hyperglycemia that is resistant to insulin analogous to human type II diabetes (Mandel *et al.*, *J. Immunol.* 120:1375-1377 (1978)).

5 The characteristics observed in these animals suggests that healing in this model may be similar to the healing observed in human diabetes (Greenhalgh, *et al.*, *Am. J. of Pathol.* 136:1235-1246 (1990)).

Genetically diabetic female C57BL/KsJ (db+/db+) mice and their non-diabetic (db+/+m) heterozygous littermates are used in this study (Jackson Laboratories). The
10 animals are purchased at 6 weeks of age and are 8 weeks old at the beginning of the study. Animals are individually housed and received food and water ad libitum. All manipulations are performed using aseptic techniques. The experiments are conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

15 Wounding protocol is performed according to previously reported methods (Tsuboi, R. and Rifkin, D.B., *J. Exp. Med.* 172:245-251 (1990)). Briefly, on the day of wounding, animals are anesthetized with an intraperitoneal injection of Avertin (0.01 mg/mL), 2,2,2-tribromoethanol and 2-methyl-2-butanol dissolved in deionized water. The dorsal region of the animal is shaved and the skin washed with 70% ethanol solution and iodine. The surgical
20 area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is then created using a Keyes tissue punch. Immediately following wounding, the surrounding skin is gently stretched to eliminate wound expansion. The wounds are left open for the duration of the experiment. Application of the treatment is given topically for 5 consecutive days commencing on the day of wounding. Prior to treatment, wounds are gently cleansed with
25 sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of surgery and at two day intervals thereafter. Wound closure is determined by daily measurement on days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no
30 longer visible and the wound is covered by a continuous epithelium.

An agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups

received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology and immunohistochemistry. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

Three groups of 10 animals each (5 diabetic and 5 non-diabetic controls) are evaluated: 1) Vehicle placebo control, 2) untreated group, and 3) treated group.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total square area of the wound. Contraction is then estimated by establishing the differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

$$[\text{Open area on day 8}] - [\text{Open area on day 1}] / [\text{Open area on day 1}]$$

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned perpendicular to the wound surface (5mm) and cut using a Reichert-Jung microtome. Routine hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds. Histologic examination of the wounds are used to assess whether the healing process and the morphologic appearance of the repaired skin is altered by treatment with an agonist or antagonist of the invention. This assessment included verification of the presence of cell accumulation, inflammatory cells, capillaries, fibroblasts, re-epithelialization and epidermal maturity (Greenhalgh, D.G. *et al.*, *Am. J. Pathol.* 136:1235 (1990)). A calibrated lens micrometer is used by a blinded observer.

Tissue sections are also stained immunohistochemically with a polyclonal rabbit anti-human keratin antibody using ABC Elite detection system. Human skin is used as a positive tissue control while non-immune IgG is used as a negative control. Keratinocyte growth is determined by evaluating the extent of reepithelialization of the wound using a calibrated lens micrometer.

Proliferating cell nuclear antigen/cyclin (PCNA) in skin specimens is demonstrated by using anti-PCNA antibody (1:50) with an ABC Elite detection system. Human colon cancer served as a positive tissue control and human brain tissue is used as a negative tissue

control. Each specimen included a section with omission of the primary antibody and substitution with non-immune mouse IgG. Ranking of these sections is based on the extent of proliferation on a scale of 0-8, the lower side of the scale reflecting slight proliferation to the higher side reflecting intense proliferation.

- 5 Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is considered significant.

B. Steroid Impaired Rat Model

- The inhibition of wound healing by steroids has been well documented in various *in vitro* and
10 *in vivo* systems (Wahl, Glucocorticoids and Wound healing. In: Anti-Inflammatory Steroid Action: Basic and Clinical Aspects. 280-302 (1989); Wahl *et al.*, *J. Immunol.* 115: 476-481 (1975); Werb *et al.*, *J. Exp. Med.* 147:1684-1694 (1978)). Glucocorticoids retard wound healing by inhibiting angiogenesis, decreasing vascular permeability (Ebert *et al.*, *Am. Intern. Med.* 37:701-705 (1952)), fibroblast proliferation, and collagen synthesis (Beck *et al.*,
15 *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978)) and producing a transient reduction of circulating monocytes (Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989)). The systemic administration of steroids to impaired wound healing is a well establish
20 phenomenon in rats (Beck *et al.*, *Growth Factors.* 5: 295-304 (1991); Haynes *et al.*, *J. Clin. Invest.* 61: 703-797 (1978); Wahl, "Glucocorticoids and wound healing", In: Antiinflammatory Steroid Action: Basic and Clinical Aspects, Academic Press, New York, pp. 280-302 (1989); Pierce *et al.*, *Proc. Natl. Acad. Sci. USA* 86: 2229-2233 (1989)).

- To demonstrate that an agonist or antagonist of the invention can accelerate the
25 healing process, the effects of multiple topical applications of the agonist or antagonist on full thickness excisional skin wounds in rats in which healing has been impaired by the systemic administration of methylprednisolone is assessed.

- Young adult male Sprague Dawley rats weighing 250-300 g (Charles River Laboratories) are used in this example. The animals are purchased at 8 weeks of age and are
30 9 weeks old at the beginning of the study. The healing response of rats is impaired by the systemic administration of methylprednisolone (17mg/kg/rat intramuscularly) at the time of wounding. Animals are individually housed and received food and water *ad libitum*. All

manipulations are performed using aseptic techniques. This study is conducted according to the rules and guidelines of Human Genome Sciences, Inc. Institutional Animal Care and Use Committee and the Guidelines for the Care and Use of Laboratory Animals.

5 The wounding protocol is followed according to section A, above. On the day of wounding, animals are anesthetized with an intramuscular injection of ketamine (50 mg/kg) and xylazine (5 mg/kg). The dorsal region of the animal is shaved and the skin washed with 70% ethanol and iodine solutions. The surgical area is dried with sterile gauze prior to wounding. An 8 mm full-thickness wound is created using a Keyes tissue punch. The wounds are left open for the duration of the experiment. Applications of the testing materials
10 are given topically once a day for 7 consecutive days commencing on the day of wounding and subsequent to methylprednisolone administration. Prior to treatment, wounds are gently cleansed with sterile saline and gauze sponges.

Wounds are visually examined and photographed at a fixed distance at the day of wounding and at the end of treatment. Wound closure is determined by daily measurement on
15 days 1-5 and on day 8. Wounds are measured horizontally and vertically using a calibrated Jameson caliper. Wounds are considered healed if granulation tissue is no longer visible and the wound is covered by a continuous epithelium.

The agonist or antagonist of the invention is administered using at a range different doses, from 4mg to 500mg per wound per day for 8 days in vehicle. Vehicle control groups
20 received 50mL of vehicle solution.

Animals are euthanized on day 8 with an intraperitoneal injection of sodium pentobarbital (300mg/kg). The wounds and surrounding skin are then harvested for histology. Tissue specimens are placed in 10% neutral buffered formalin in tissue cassettes between biopsy sponges for further processing.

25 Four groups of 10 animals each (5 with methylprednisolone and 5 without glucocorticoid) are evaluated: 1) Untreated group 2) Vehicle placebo control 3) treated groups.

Wound closure is analyzed by measuring the area in the vertical and horizontal axis and obtaining the total area of the wound. Closure is then estimated by establishing the
30 differences between the initial wound area (day 0) and that of post treatment (day 8). The wound area on day 1 is 64mm², the corresponding size of the dermal punch. Calculations are made using the following formula:

[Open area on day 8] - [Open area on day 1] / [Open area on day 1]

Specimens are fixed in 10% buffered formalin and paraffin embedded blocks are sectioned
5 perpendicular to the wound surface (5mm) and cut using an Olympus microtome. Routine
hematoxylin-eosin (H&E) staining is performed on cross-sections of bisected wounds.
Histologic examination of the wounds allows assessment of whether the healing process and
the morphologic appearance of the repaired skin is improved by treatment with an agonist or
antagonist of the invention. A calibrated lens micrometer is used by a blinded observer to
10 determine the distance of the wound gap.

Experimental data are analyzed using an unpaired t test. A p value of < 0.05 is
considered significant.

The studies described in this example tested activity of agonists or antagonists of the
invention. However, one skilled in the art could easily modify the exemplified studies to test
15 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 29: Lymphadema Animal Model

The purpose of this experimental approach is to create an appropriate and consistent
20 lymphedema model for testing the therapeutic effects of an agonist or antagonist of the
invention in lymphangiogenesis and re-establishment of the lymphatic circulatory system in
the rat hind limb. Effectiveness is measured by swelling volume of the affected limb,
quantification of the amount of lymphatic vasculature, total blood plasma protein, and
histopathology. Acute lymphedema is observed for 7-10 days. Perhaps more importantly,
25 the chronic progress of the edema is followed for up to 3-4 weeks.

Prior to beginning surgery, blood sample is drawn for protein concentration analysis.
Male rats weighing approximately ~350g are dosed with Pentobarbital. Subsequently, the
right legs are shaved from knee to hip. The shaved area is swabbed with gauze soaked in
70% EtOH. Blood is drawn for serum total protein testing. Circumference and volumetric
30 measurements are made prior to injecting dye into paws after marking 2 measurement levels
(0.5 cm above heel, at mid-pt of dorsal paw). The intradermal dorsum of both right and left
paws are injected with 0.05 ml of 1% Evan's Blue. Circumference and volumetric

measurements are then made following injection of dye into paws.

Using the knee joint as a landmark, a mid-leg inguinal incision is made circumferentially allowing the femoral vessels to be located. Forceps and hemostats are used to dissect and separate the skin flaps. After locating the femoral vessels, the lymphatic vessel
5 that runs along side and underneath the vessel(s) is located. The main lymphatic vessels in this area are then electrically coagulated or suture ligated.

Using a microscope, muscles in back of the leg (near the semitendinosus and adductors) are bluntly dissected. The popliteal lymph node is then located. The 2 proximal and 2 distal lymphatic vessels and distal blood supply of the popliteal node are then and
10 ligated by suturing. The popliteal lymph node, and any accompanying adipose tissue, is then removed by cutting connective tissues.

Care is taken to control any mild bleeding resulting from this procedure. After lymphatics are occluded, the skin flaps are sealed by using liquid skin (Vetbond) (AJ Buck). The separated skin edges are sealed to the underlying muscle tissue while leaving a gap of
15 ~0.5 cm around the leg. Skin also may be anchored by suturing to underlying muscle when necessary.

To avoid infection, animals are housed individually with mesh (no bedding). Recovering animals are checked daily through the optimal edematous peak, which typically occurred by day 5-7. The plateau edematous peak are then observed. To evaluate the
20 intensity of the lymphedema, the circumference and volumes of 2 designated places on each paw before operation and daily for 7 days are measured. The effect plasma proteins on lymphedema is determined and whether protein analysis is a useful testing perimeter is also investigated. The weights of both control and edematous limbs are evaluated at 2 places. Analysis is performed in a blind manner.

25 **Circumference Measurements:** Under brief gas anesthetic to prevent limb movement, a cloth tape is used to measure limb circumference. Measurements are done at the ankle bone and dorsal paw by 2 different people then those 2 readings are averaged. Readings are taken from both control and edematous limbs.

30 **Volumetric Measurements:** On the day of surgery, animals are anesthetized with Pentobarbital and are tested prior to surgery. For daily volumetrics animals are under brief halothane anesthetic (rapid immobilization and quick recovery), both legs are shaved and equally marked using waterproof marker on legs. Legs are first dipped in water, then dipped

into instrument to each marked level then measured by Buxco edema software(Chen/Victor). Data is recorded by one person, while the other is dipping the limb to marked area.

Blood-plasma protein measurements: Blood is drawn, spun, and serum separated prior to surgery and then at conclusion for total protein and Ca²⁺ comparison.

5 Limb Weight Comparison: After drawing blood, the animal is prepared for tissue collection. The limbs are amputated using a quillitine, then both experimental and control legs are cut at the ligature and weighed. A second weighing is done as the tibio-cacaneal joint is disarticulated and the foot is weighed.

10 Histological Preparations: The transverse muscle located behind the knee (popliteal) area is dissected and arranged in a metal mold, filled with freezeGel, dipped into cold methylbutane, placed into labeled sample bags at - 80EC until sectioning. Upon sectioning, the muscle is observed under fluorescent microscopy for lymphatics..

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
15 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 30: Suppression of TNF alpha-induced adhesion molecule expression by a Agonist or Antagonist of the Invention

20 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and endothelial
25 leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor participate in the modulation of the expression of these CAMs.

30 Tumor necrosis factor alpha (TNF- α), a potent proinflammatory cytokine, is a stimulator of all three CAMs on endothelial cells and may be involved in a wide variety of inflammatory responses, often resulting in a pathological outcome.

The potential of an agonist or antagonist of the invention to mediate a suppression of TNF- α induced CAM expression can be examined. A modified ELISA assay which uses ECs as a solid phase absorbent is employed to measure the amount of CAM expression on TNF- α treated ECs when co-stimulated with a member of the FGF family of proteins.

5 To perform the experiment, human umbilical vein endothelial cell (HUVEC) cultures are obtained from pooled cord harvests and maintained in growth medium (EGM-2; Clonetics, San Diego, CA) supplemented with 10% FCS and 1% penicillin/streptomycin in a 37 degree C humidified incubator containing 5% CO₂. HUVECs are seeded in 96-well plates at concentrations of 1×10^4 cells/well in EGM medium at 37 degree C for 18-24 hrs or
10 until confluent. The monolayers are subsequently washed 3 times with a serum-free solution of RPMI-1640 supplemented with 100 U/ml penicillin and 100 mg/ml streptomycin, and treated with a given cytokine and/or growth factor(s) for 24 h at 37 degree C. Following incubation, the cells are then evaluated for CAM expression.

Human Umbilical Vein Endothelial cells (HUVECs) are grown in a standard 96 well
15 plate to confluence. Growth medium is removed from the cells and replaced with 90 μ l of 199 Medium (10% FBS). Samples for testing and positive or negative controls are added to the plate in triplicate (in 10 μ l volumes). Plates are incubated at 37 degree C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 μ l of 0.1% paraformaldehyde-PBS(with Ca⁺⁺ and Mg⁺⁺) is added
20 to each well. Plates are held at 4°C for 30 min.

Fixative is then removed from the wells and wells are washed 1X with PBS(+Ca,Mg)+0.5% BSA and drained. Do not allow the wells to dry. Add 10 μ l of diluted primary antibody to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 μ g/ml (1:10 dilution of 0.1
25 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA.

Then add 20 μ l of diluted ExtrAvidin-Alkaline Phosphatase (1:5,000 dilution) to each well and incubated at 37°C for 30 min. Wells are washed X3 with PBS(+Ca,Mg)+0.5% BSA. 1 tablet of p-Nitrophenol Phosphate pNPP is dissolved in 5 ml of glycine buffer (pH
30 10.4). 100 μ l of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 μ l of each dilution is added to triplicate

wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 μ l of pNPN reagent must then be added to each of the standard wells. The plate must be incubated at 37°C for 4h. A volume of 50 μ l of 3M NaOH is added to all wells. The results are quantified on a plate reader at 405 nm. The background subtraction option is used on
5 blank wells filled with glycine buffer only. The template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

The studies described in this example tested activity of agonists or antagonists of the invention. However, one skilled in the art could easily modify the exemplified studies to test
10 the activity of polynucleotides or polypeptides of the invention (e.g., gene therapy).

Example 31: Production Of Polypeptide of the Invention For High-Throughput Screening Assays

15 The following protocol produces a supernatant containing polypeptide of the present invention to be tested. This supernatant can then be used in the Screening Assays described in Examples 33-42.

First, dilute Poly-D-Lysine (644 587 Boehringer-Mannheim) stock solution (1mg/ml in PBS) 1:20 in PBS (w/o calcium or magnesium 17-516F Biowhittaker) for a working
20 solution of 50ug/ml. Add 200 μ l of this solution to each well (24 well plates) and incubate at RT for 20 minutes. Be sure to distribute the solution over each well (note: a 12-channel pipetter may be used with tips on every other channel). Aspirate off the Poly-D-Lysine solution and rinse with 1ml PBS (Phosphate Buffered Saline). The PBS should remain in the well until just prior to plating the cells and plates may be poly-lysine coated in advance for
25 up to two weeks.

Plate 293T cells (do not carry cells past P+20) at 2×10^5 cells/well in .5ml DMEM(Dulbecco's Modified Eagle Medium)(with 4.5 G/L glucose and L-glutamine (12-604F Biowhittaker))/10% heat inactivated FBS(14-503F Biowhittaker)/1x Penstrep(17-602E Biowhittaker). Let the cells grow overnight.

30 The next day, mix together in a sterile solution basin: 300 μ l Lipofectamine (18324-012 Gibco/BRL) and 5ml Optimem I (31985070 Gibco/BRL)/96-well plate. With a small volume multi-channel pipetter, aliquot approximately 2ug of an expression vector containing

a polynucleotide insert, produced by the methods described in Examples 8-10, into an appropriately labeled 96-well round bottom plate. With a multi-channel pipetter, add 50ul of the Lipofectamine/Optimem I mixture to each well. Pipette up and down gently to mix. Incubate at RT 15-45 minutes. After about 20 minutes, use a multi-channel pipetter to add
5 150ul Optimem I to each well. As a control, one plate of vector DNA lacking an insert should be transfected with each set of transfections.

Preferably, the transfection should be performed by tag-teaming the following tasks. By tag-teaming, hands on time is cut in half, and the cells do not spend too much time on PBS. First, person A aspirates off the media from four 24-well plates of cells, and then
10 person B rinses each well with .5-1ml PBS. Person A then aspirates off PBS rinse, and person B, using a 12-channel pipetter with tips on every other channel, adds the 200ul of DNA/Lipofectamine/Optimem I complex to the odd wells first, then to the even wells, to each row on the 24-well plates. Incubate at 37 degree C for 6 hours.

While cells are incubating, prepare appropriate media, either 1%BSA in DMEM with
15 1x penstrep, or HGS CHO-5 media (116.6 mg/L of CaCl₂ (anhyd); 0.00130 mg/L CuSO₄-5H₂O; 0.050 mg/L of Fe(NO₃)₃-9H₂O; 0.417 mg/L of FeSO₄-7H₂O; 311.80 mg/L of Kcl; 28.64 mg/L of MgCl₂; 48.84 mg/L of MgSO₄; 6995.50 mg/L of NaCl; 2400.0 mg/L of NaHCO₃; 62.50 mg/L of NaH₂PO₄-H₂O; 71.02 mg/L of Na₂HPO₄; .4320 mg/L of ZnSO₄-7H₂O; .002 mg/L of Arachidonic Acid; 1.022 mg/L of Cholesterol; .070 mg/L of DL-alpha-
20 Tocopherol-Acetate; 0.0520 mg/L of Linoleic Acid; 0.010 mg/L of Linolenic Acid; 0.010 mg/L of Myristic Acid; 0.010 mg/L of Oleic Acid; 0.010 mg/L of Palmitic Acid; 0.010 mg/L of Palmitic Acid; 100 mg/L of Pluronic F-68; 0.010 mg/L of Stearic Acid; 2.20 mg/L of Tween 80; 4551 mg/L of D-Glucose; 130.85 mg/ml of L- Alanine; 147.50 mg/ml of L- Arginine-HCL; 7.50 mg/ml of L-Asparagine-H₂O; 6.65 mg/ml of L-Aspartic Acid; 29.56
25 mg/ml of L-Cystine-2HCL-H₂O; 31.29 mg/ml of L-Cystine-2HCL; 7.35 mg/ml of L- Glutamic Acid; 365.0 mg/ml of L-Glutamine; 18.75 mg/ml of Glycine; 52.48 mg/ml of L- Histidine-HCL-H₂O; 106.97 mg/ml of L-Isoleucine; 111.45 mg/ml of L-Leucine; 163.75 mg/ml of L-Lysine HCL; 32.34 mg/ml of L-Methionine; 68.48 mg/ml of L-Phenylalanine; 40.0 mg/ml of L-Proline; 26.25 mg/ml of L-Serine; 101.05 mg/ml of L-Threonine; 19.22
30 mg/ml of L-Tryptophan; 91.79 mg/ml of L-Tyrosine-2Na-2H₂O; and 99.65 mg/ml of L-

Valine; 0.0035 mg/L of Biotin; 3.24 mg/L of D-Ca Pantothenate; 11.78 mg/L of Choline Chloride; 4.65 mg/L of Folic Acid; 15.60 mg/L of i-Inositol; 3.02 mg/L of Niacinamide; 3.00 mg/L of Pyridoxal HCL; 0.031 mg/L of Pyridoxine HCL; 0.319 mg/L of Riboflavin; 3.17 mg/L of Thiamine HCL; 0.365 mg/L of Thymidine; 0.680 mg/L of Vitamin B₁₂; 25 mM of
5 HEPES Buffer; 2.39 mg/L of Na Hypoxanthine; 0.105 mg/L of Lipoic Acid; 0.081 mg/L of Sodium Putrescine-2HCL; 55.0 mg/L of Sodium Pyruvate; 0.0067 mg/L of Sodium Selenite; 20uM of Ethanolamine; 0.122 mg/L of Ferric Citrate; 41.70 mg/L of Methyl-B-Cyclodextrin complexed with Linoleic Acid; 33.33 mg/L of Methyl-B-Cyclodextrin complexed with Oleic Acid; 10 mg/L of Methyl-B-Cyclodextrin complexed with Retinal Acetate. Adjust
10 osmolarity to 327 mOsm) with 2mm glutamine and 1x penstrep. (BSA (81-068-3 Bayer) 100gm dissolved in 1L DMEM for a 10% BSA stock solution). Filter the media and collect 50 ul for endotoxin assay in 15ml polystyrene conical.

The transfection reaction is terminated, preferably by tag-teaming, at the end of the incubation period. Person A aspirates off the transfection media, while person B adds 1.5ml
15 appropriate media to each well. Incubate at 37 degree C for 45 or 72 hours depending on the media used: 1%BSA for 45 hours or CHO-5 for 72 hours.

On day four, using a 300ul multichannel pipetter, aliquot 600ul in one 1ml deep well plate and the remaining supernatant into a 2ml deep well. The supernatants from each well can then be used in the assays described in Examples 33-40.

20 It is specifically understood that when activity is obtained in any of the assays described below using a supernatant, the activity originates from either the polypeptide of the present invention directly (e.g., as a secreted protein) or by polypeptide of the present invention inducing expression of other proteins, which are then secreted into the supernatant. Thus, the invention further provides a method of identifying the protein in the supernatant
25 characterized by an activity in a particular assay.

Example 32: Construction of GAS Reporter Construct

30 One signal transduction pathway involved in the differentiation and proliferation of cells is called the Jaks-STATs pathway. Activated proteins in the Jaks-STATs pathway bind to gamma activation site "GAS" elements or interferon-sensitive responsive element ("ISRE"), located in the promoter of many genes. The binding of a protein to these elements

alter the expression of the associated gene.

GAS and ISRE elements are recognized by a class of transcription factors called Signal Transducers and Activators of Transcription, or "STATs." There are six members of the STATs family. Stat1 and Stat3 are present in many cell types, as is Stat2 (as response to IFN-alpha is widespread). Stat4 is more restricted and is not in many cell types though it has been found in T helper class I, cells after treatment with IL-12. Stat5 was originally called mammary growth factor, but has been found at higher concentrations in other cells including myeloid cells. It can be activated in tissue culture cells by many cytokines.

The STATs are activated to translocate from the cytoplasm to the nucleus upon tyrosine phosphorylation by a set of kinases known as the Janus Kinase ("Jaks") family. Jaks represent a distinct family of soluble tyrosine kinases and include Tyk2, Jak1, Jak2, and Jak3. These kinases display significant sequence similarity and are generally catalytically inactive in resting cells.

The Jaks are activated by a wide range of receptors summarized in the Table below. (Adapted from review by Schidler and Darnell, Ann. Rev. Biochem. 64:621-51 (1995).) A cytokine receptor family, capable of activating Jaks, is divided into two groups: (a) Class 1 includes receptors for IL-2, IL-3, IL-4, IL-6, IL-7, IL-9, IL-11, IL-12, IL-15, Epo, PRL, GH, G-CSF, GM-CSF, LIF, CNTF, and thrombopoietin; and (b) Class 2 includes IFN-a, IFN-g, and IL-10. The Class 1 receptors share a conserved cysteine motif (a set of four conserved cysteines and one tryptophan) and a WSXWS motif (a membrane proximal region encoding Trp-Ser-Xxx-Trp-Ser (SEQ ID NO:838)).

Thus, on binding of a ligand to a receptor, Jaks are activated, which in turn activate STATs, which then translocate and bind to GAS elements. This entire process is encompassed in the Jaks-STATs signal transduction pathway.

Therefore, activation of the Jaks-STATs pathway, reflected by the binding of the GAS or the ISRE element, can be used to indicate proteins involved in the proliferation and differentiation of cells. For example, growth factors and cytokines are known to activate the Jaks-STATs pathway. (See Table below.) Thus, by using GAS elements linked to reporter molecules, activators of the Jaks-STATs pathway can be identified.

| <u>Ligand</u> | <u>JAKs</u> | | | | <u>STATS GAS(elements) or ISRE</u> | |
|------------------------------|-------------|-------------|-------------|-------------|------------------------------------|---------------------|
| | <u>tyk2</u> | <u>Jak1</u> | <u>Jak2</u> | <u>Jak3</u> | | |
| <u>IFN family</u> | | | | | | |
| 5 IFN-a/B | + | + | - | - | 1,2,3 | ISRE |
| IFN-g | | + | + | - | 1 | GAS (IRF1>Lys6>IFP) |
| Il-10 | + | ? | ? | - | 1,3 | |
| <u>gp130 family</u> | | | | | | |
| 10 IL-6 (Pleiotrohic) | + | + | + | ? | 1,3 | GAS (IRF1>Lys6>IFP) |
| Il-11(Pleiotrohic) | ? | + | ? | ? | 1,3 | |
| OnM(Pleiotrohic) | ? | + | + | ? | 1,3 | |
| LIF(Pleiotrohic) | ? | + | + | ? | 1,3 | |
| CNTF(Pleiotrohic) | -/+ | + | + | ? | 1,3 | |
| 15 G-CSF(Pleiotrohic) | ? | + | ? | ? | 1,3 | |
| IL-12(Pleiotrohic) | + | - | + | + | 1,3 | |
| <u>g-C family</u> | | | | | | |
| IL-2 (lymphocytes) | - | + | - | + | 1,3,5 | GAS |
| 20 IL-4 (lymph/myeloid) | - | + | - | + | 6 | GAS (IRF1 = IFP |
| >>Ly6)(IgH) | | | | | | |
| IL-7 (lymphocytes) | - | + | - | + | 5 | GAS |
| IL-9 (lymphocytes) | - | + | - | + | 5 | GAS |
| IL-13 (lymphocyte) | - | + | ? | ? | 6 | GAS |
| 25 IL-15 | ? | + | ? | + | 5 | GAS |
| <u>gp140 family</u> | | | | | | |
| IL-3 (myeloid) | - | - | + | - | 5 | GAS (IRF1>IFP>>Ly6) |
| IL-5 (myeloid) | - | - | + | - | 5 | GAS |
| 30 GM-CSF (myeloid) | - | - | + | - | 5 | GAS |
| <u>Growth hormone family</u> | | | | | | |
| GH | ? | - | + | - | 5 | |
| PRL | ? | +/- | + | - | 1,3,5 | |
| 35 EPO | ? | - | + | - | 5 | GAS(B- |

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CAS>IRF1=IFP>>Ly6)

Receptor Tyrosine Kinases

| | | | | | | | |
|---|-------|---|---|---|---|-----|----------------|
| | EGF | ? | + | + | - | 1,3 | GAS (IRF1) |
| 5 | PDGF | ? | + | + | - | 1,3 | |
| | CSF-1 | ? | + | + | - | 1,3 | GAS (not IRF1) |

To construct a synthetic GAS containing promoter element, which is used in the Biological Assays described in Examples 33-34, a PCR based strategy is employed to generate a GAS-SV40 promoter sequence. The 5' primer contains four tandem copies of the GAS binding site found in the IRF1 promoter and previously demonstrated to bind STATs upon induction with a range of cytokines (Rothman et al., Immunity 1:457-468 (1994).), although other GAS or ISRE elements can be used instead. The 5' primer also contains 18bp of sequence complementary to the SV40 early promoter sequence and is flanked with an XhoI site. The sequence of the 5' primer is:

5' : GCGCCTCGAGATTTCCCGAAATCTAGATTTCCCGAAATGATTTCCCG
GAAATGATTTCCCGAAATATCTGCCATCTCAATTAG:3' (SEQ ID NO:839)

The downstream primer is complementary to the SV40 promoter and is flanked with a Hind III site: 5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:840)

PCR amplification is performed using the SV40 promoter template present in the B-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI/Hind III and subcloned into BLSK2-. (Stratagene.) Sequencing with forward and reverse primers confirms that the insert contains the following sequence:

5' : CTCGAGATTTCCCGAAATCTAGATTTCCCGAAATGATTTCCCGAAA
TGATTTCCCGAAATATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCG
CCCCTAACTCCGCCATCCCGCCCCTAACTCCGCCCAGTTCCGCCATTCT
CCGCCCCATGGCTGACTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCC
TCGGCCTCTGAGCTATTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTA
GGCTTTTGCAAAAAAGCTT:3' (SEQ ID NO:841)

With this GAS promoter element linked to the SV40 promoter, a GAS:SEAP2 reporter construct is next engineered. Here, the reporter molecule is a secreted alkaline phosphatase, or "SEAP." Clearly, however, any reporter molecule can be instead of SEAP, in this or in any of the other Examples. Well known reporter molecules that can be used instead of SEAP include chloramphenicol

acetyltransferase (CAT), luciferase, alkaline phosphatase, B-galactosidase, green fluorescent protein (GFP), or any protein detectable by an antibody.

The above sequence confirmed synthetic GAS-SV40 promoter element is subcloned into the pSEAP-Promoter vector obtained from Clontech using HindIII and XhoI, effectively replacing the SV40 promoter with the amplified GAS:SV40 promoter element, to create the GAS-SEAP vector. However, this vector does not contain a neomycin resistance gene, and therefore, is not preferred for mammalian expression systems.

Thus, in order to generate mammalian stable cell lines expressing the GAS-SEAP reporter, the GAS-SEAP cassette is removed from the GAS-SEAP vector using SalI and NotI, and inserted into a backbone vector containing the neomycin resistance gene, such as pGFP-1 (Clontech), using these restriction sites in the multiple cloning site, to create the GAS-SEAP/Neo vector. Once this vector is transfected into mammalian cells, this vector can then be used as a reporter molecule for GAS binding as described in Examples 33-34.

Other constructs can be made using the above description and replacing GAS with a different promoter sequence. For example, construction of reporter molecules containing NFK-B and EGR promoter sequences are described in Examples 35 and 36. However, many other promoters can be substituted using the protocols described in these Examples. For instance, SRE, IL-2, NFAT, or Osteocalcin promoters can be substituted, alone or in combination (e.g., GAS/NF-KB/EGR, GAS/NF-KB, IL-2/NFAT, or NF-KB/GAS). Similarly, other cell lines can be used to test reporter construct activity, such as HELA (epithelial), HUVEC (endothelial), Reh (B-cell), Saos-2 (osteoblast), HUVAC (aortic), or Cardiomyocyte.

Example 33: High-Throughput Screening Assay for T-cell Activity.

The following protocol is used to assess T-cell activity by identifying factors, and determining whether supernate containing a polypeptide of the invention proliferates and/or differentiates T-cells. T-cell activity is assessed using the

GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The T-cell used in this assay is Jurkat T-cells (ATCC Accession No. TIB-152), although Molt-3 cells (ATCC Accession No. CRL-1552) and Molt-4 cells (ATCC
5 Accession No. CRL-1582) cells can also be used.

Jurkat T-cells are lymphoblastic CD4+ Th1 helper cells. In order to generate stable cell lines, approximately 2 million Jurkat cells are transfected with the GAS-SEAP/neo vector using DMRIE-C (Life Technologies)(transfection procedure described below). The transfected cells are seeded to a density of approximately
10 20,000 cells per well and transfectants resistant to 1 mg/ml gentamicin selected. Resistant colonies are expanded and then tested for their response to increasing concentrations of interferon gamma. The dose response of a selected clone is demonstrated.

Specifically, the following protocol will yield sufficient cells for 75 wells
15 containing 200 ul of cells. Thus, it is either scaled up, or performed in multiple to generate sufficient cells for multiple 96 well plates. Jurkat cells are maintained in RPMI + 10% serum with 1%Pen-Strep. Combine 2.5 mls of OPTI-MEM (Life Technologies) with 10 ug of plasmid DNA in a T25 flask. Add 2.5 ml OPTI-MEM containing 50 ul of DMRIE-C and incubate at room temperature for 15-45 mins.

20 During the incubation period, count cell concentration, spin down the required number of cells (10^7 per transfection), and resuspend in OPTI-MEM to a final concentration of 10^7 cells/ml. Then add 1ml of 1×10^7 cells in OPTI-MEM to T25 flask and incubate at 37 degree C for 6 hrs. After the incubation, add 10 ml of RPMI + 15% serum.

25 The Jurkat:GAS-SEAP stable reporter lines are maintained in RPMI + 10% serum, 1 mg/ml Gentamicin, and 1% Pen-Strep. These cells are treated with supernatants containing polypeptide of the present invention or polypeptide of the present invention induced polypeptides as produced by the protocol described in Example 31.

30 On the day of treatment with the supernatant, the cells should be washed and

resuspended in fresh RPMI + 10% serum to a density of 500,000 cells per ml. The exact number of cells required will depend on the number of supernatants being screened. For one 96 well plate, approximately 10 million cells (for 10 plates, 100 million cells) are required.

5 Transfer the cells to a triangular reservoir boat, in order to dispense the cells into a 96 well dish, using a 12 channel pipette. Using a 12 channel pipette, transfer 200 ul of cells into each well (therefore adding 100,000 cells per well).

 After all the plates have been seeded, 50 ul of the supernatants are transferred directly from the 96 well plate containing the supernatants into each well using a 12
10 channel pipette. In addition, a dose of exogenous interferon gamma (0.1, 1.0, 10 ng) is added to wells H9, H10, and H11 to serve as additional positive controls for the assay.

 The 96 well dishes containing Jurkat cells treated with supernatants are placed in an incubator for 48 hrs (note: this time is variable between 48-72 hrs). 35 ul
15 samples from each well are then transferred to an opaque 96 well plate using a 12 channel pipette. The opaque plates should be covered (using sellophane covers) and stored at -20 degree C until SEAP assays are performed according to Example 37. The plates containing the remaining treated cells are placed at 4 degree C and serve as a source of material for repeating the assay on a specific well if desired.

20 As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate Jurkat T cells. Over 30 fold induction is typically observed in the positive control wells.

 The above protocol may be used in the generation of both transient, as well as, stable transfected cells, which would be apparent to those of skill in the art.

25

Example 34: High-Throughput Screening Assay Identifying Myeloid Activity

 The following protocol is used to assess myeloid activity of polypeptide of the present invention by determining whether polypeptide of the present invention
30 proliferates and/or differentiates myeloid cells. Myeloid cell activity is assessed using

the GAS/SEAP/Neo construct produced in Example 32. Thus, factors that increase SEAP activity indicate the ability to activate the Jaks-STATS signal transduction pathway. The myeloid cell used in this assay is U937, a pre-monocyte cell line, although TF-1, HL60, or KG1 can be used.

5 To transiently transfect U937 cells with the GAS/SEAP/Neo construct produced in Example 32, a DEAE-Dextran method (Kharbanda et. al., 1994, Cell Growth & Differentiation, 5:259-265) is used. First, harvest 2×10^7 U937 cells and wash with PBS. The U937 cells are usually grown in RPMI 1640 medium containing 10% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml
10 penicillin and 100 mg/ml streptomycin.

Next, suspend the cells in 1 ml of 20 mM Tris-HCl (pH 7.4) buffer containing 0.5 mg/ml DEAE-Dextran, 8 ug GAS-SEAP2 plasmid DNA, 140 mM NaCl, 5 mM KCl, 375 uM $\text{Na}_2\text{HPO}_4 \cdot 7\text{H}_2\text{O}$, 1 mM MgCl_2 , and 675 uM CaCl_2 . Incubate at 37 degrees C for 45 min.

15 Wash the cells with RPMI 1640 medium containing 10% FBS and then resuspend in 10 ml complete medium and incubate at 37 degree C for 36 hr.

The GAS-SEAP/U937 stable cells are obtained by growing the cells in 400 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 400 ug/ml G418 for couple of passages.

20 These cells are tested by harvesting 1×10^8 cells (this is enough for ten 96-well plates assay) and wash with PBS. Suspend the cells in 200 ml above described growth medium, with a final density of 5×10^5 cells/ml. Plate 200 ul cells per well in the 96-well plate (or 1×10^5 cells/well).

Add 50 ul of the supernatant prepared by the protocol described in Example
25 31. Incubate at 37 degree C for 48 to 72 hr. As a positive control, 100 Unit/ml interferon gamma can be used which is known to activate U937 cells. Over 30 fold induction is typically observed in the positive control wells. SEAP assay the supernatant according to the protocol described in Example 37.

30 *Example 35: High-Throughput Screening Assay Identifying Neuronal Activity.*

When cells undergo differentiation and proliferation, a group of genes are activated through many different signal transduction pathways. One of these genes, EGR1 (early growth response gene 1), is induced in various tissues and cell types upon activation. The promoter of EGR1 is responsible for such induction. Using the EGR1 promoter linked to reporter molecules, activation of cells can be assessed by polypeptide of the present invention.

Particularly, the following protocol is used to assess neuronal activity in PC12 cell lines. PC12 cells (rat phenochromocytoma cells) are known to proliferate and/or differentiate by activation with a number of mitogens, such as TPA (tetradecanoyl phorbol acetate), NGF (nerve growth factor), and EGF (epidermal growth factor). The EGR1 gene expression is activated during this treatment. Thus, by stably transfecting PC12 cells with a construct containing an EGR promoter linked to SEAP reporter, activation of PC12 cells by polypeptide of the present invention can be assessed.

The EGR/SEAP reporter construct can be assembled by the following protocol. The EGR-1 promoter sequence (-633 to +1)(Sakamoto K et al., Oncogene 6:867-871 (1991)) can be PCR amplified from human genomic DNA using the following primers:

5' GCGCTCGAGGGATGACAGCGATAGAACCCCGG -3' (SEQ ID NO:842)

5' GCGAAGCTTCGCGACTCCCCGGATCCGCCTC-3' (SEQ ID NO:843)

Using the GAS:SEAP/Neo vector produced in Example 32, EGR1 amplified product can then be inserted into this vector. Linearize the GAS:SEAP/Neo vector using restriction enzymes XhoI/HindIII, removing the GAS/SV40 stuffer. Restrict the EGR1 amplified product with these same enzymes. Ligate the vector and the EGR1 promoter.

To prepare 96 well-plates for cell culture, two mls of a coating solution (1:30 dilution of collagen type I (Upstate Biotech Inc. Cat#08-115) in 30% ethanol (filter sterilized)) is added per one 10 cm plate or 50 ml per well of the 96-well plate, and

allowed to air dry for 2 hr.

PC12 cells are routinely grown in RPMI-1640 medium (Bio Whittaker) containing 10% horse serum (JRH BIOSCIENCES, Cat. # 12449-78P), 5% heat-inactivated fetal bovine serum (FBS) supplemented with 100 units/ml penicillin and 100 ug/ml streptomycin on a precoated 10 cm tissue culture dish. One to four split is done every three to four days. Cells are removed from the plates by scraping and resuspended with pipetting up and down for more than 15 times.

Transfect the EGR/SEAP/Neo construct into PC12 using the Lipofectamine protocol described in Example 31. EGR-SEAP/PC12 stable cells are obtained by growing the cells in 300 ug/ml G418. The G418-free medium is used for routine growth but every one to two months, the cells should be re-grown in 300 ug/ml G418 for couple of passages.

To assay for neuronal activity, a 10 cm plate with cells around 70 to 80% confluent is screened by removing the old medium. Wash the cells once with PBS (Phosphate buffered saline). Then starve the cells in low serum medium (RPMI-1640 containing 1% horse serum and 0.5% FBS with antibiotics) overnight.

The next morning, remove the medium and wash the cells with PBS. Scrape off the cells from the plate, suspend the cells well in 2 ml low serum medium. Count the cell number and add more low serum medium to reach final cell density as 5×10^5 cells/ml.

Add 200 ul of the cell suspension to each well of 96-well plate (equivalent to 1×10^5 cells/well). Add 50 ul supernatant produced by Example 31, 37 degree C for 48 to 72 hr. As a positive control, a growth factor known to activate PC12 cells through EGR can be used, such as 50 ng/ul of Neuronal Growth Factor (NGF). Over fifty-fold induction of SEAP is typically seen in the positive control wells. SEAP assay the supernatant according to Example 37.

Example 36: High-Throughput Screening Assay for T-cell Activity

NF-KB (Nuclear Factor KB) is a transcription factor activated by a wide

variety of agents including the inflammatory cytokines IL-1 and TNF, CD30 and CD40, lymphotoxin-alpha and lymphotoxin-beta, by exposure to LPS or thrombin, and by expression of certain viral gene products. As a transcription factor, NF-KB regulates the expression of genes involved in immune cell activation, control of apoptosis (NF- KB appears to shield cells from apoptosis), B and T-cell development, anti-viral and antimicrobial responses, and multiple stress responses.

In non-stimulated conditions, NF- KB is retained in the cytoplasm with I-KB (Inhibitor KB). However, upon stimulation, I- KB is phosphorylated and degraded, causing NF- KB to shuttle to the nucleus, thereby activating transcription of target genes. Target genes activated by NF- KB include IL-2, IL-6, GM-CSF, ICAM-1 and class I MHC.

Due to its central role and ability to respond to a range of stimuli, reporter constructs utilizing the NF-KB promoter element are used to screen the supernatants produced in Example 31. Activators or inhibitors of NF-KB would be useful in treating, preventing, and/or diagnosing diseases. For example, inhibitors of NF-KB could be used to treat those diseases related to the acute or chronic activation of NF-KB, such as rheumatoid arthritis.

To construct a vector containing the NF-KB promoter element, a PCR based strategy is employed. The upstream primer contains four tandem copies of the NF-KB binding site (GGGGACTTTCCC) (SEQ ID NO:844), 18 bp of sequence complementary to the 5' end of the SV40 early promoter sequence, and is flanked with an XhoI site:

5':GCGGCCTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGAC
TTTCCATCCTGCCATCTCAATTAG:3' (SEQ ID NO:845)

The downstream primer is complementary to the 3' end of the SV40 promoter and is flanked with a Hind III site:

5':GCGGCAAGCTTTTTGCAAAGCCTAGGC:3' (SEQ ID NO:840)

PCR amplification is performed using the SV40 promoter template present in the pB-gal:promoter plasmid obtained from Clontech. The resulting PCR fragment is digested with XhoI and Hind III and subcloned into BLSK2-. (Stratagene)

Sequencing with the T7 and T3 primers confirms the insert contains the following sequence:

5':CTCGAGGGGACTTTCCCGGGGACTTTCCGGGGACTTTCCGGGGACTTTCC
ATCTGCCATCTCAATTAGTCAGCAACCATAGTCCCGCCCCTAACTCCGCCC
5 ATCCCGCCCCTAACTCCGCCCAGTTCCGCCCATTCTCCGCCCCATGGCTGA
CTAATTTTTTTTATTTATGCAGAGGCCGAGGCCGCCTCGGCCTCTGAGCTA
TTCCAGAAGTAGTGAGGAGGCTTTTTTGGAGGCCTAGGCTTTTGCAAAAA
GCTT:3' (SEQ ID NO:846)

Next, replace the SV40 minimal promoter element present in the pSEAP2-
10 promoter plasmid (Clontech) with this NF-KB/SV40 fragment using XhoI and
HindIII. However, this vector does not contain a neomycin resistance gene, and
therefore, is not preferred for mammalian expression systems.

In order to generate stable mammalian cell lines, the NF-KB/SV40/SEAP
cassette is removed from the above NF-KB/SEAP vector using restriction enzymes
15 SalI and NotI, and inserted into a vector containing neomycin resistance. Particularly,
the NF-KB/SV40/SEAP cassette was inserted into pGFP-1 (Clontech), replacing the
GFP gene, after restricting pGFP-1 with SalI and NotI.

Once NF-KB/SV40/SEAP/Neo vector is created, stable Jurkat T-cells are
created and maintained according to the protocol described in Example 33. Similarly,
20 the method for assaying supernatants with these stable Jurkat T-cells is also described
in Example 33. As a positive control, exogenous TNF alpha (0.1, 1, 10 ng) is added to
wells H9, H10, and H11, with a 5-10 fold activation typically observed.

Example 37: Assay for SEAP Activity

25

As a reporter molecule for the assays described in Examples 33-36, SEAP
activity is assayed using the Tropix Phospho-light Kit (Cat. BP-400) according to the
following general procedure. The Tropix Phospho-light Kit supplies the Dilution,
Assay, and Reaction Buffers used below.

30

Prime a dispenser with the 2.5x Dilution Buffer and dispense 15 ul of 2.5x

dilution buffer into Optiplates containing 35 ul of a supernatant. Seal the plates with a plastic sealer and incubate at 65 degree C for 30 min. Separate the Optiplates to avoid uneven heating.

5 Cool the samples to room temperature for 15 minutes. Empty the dispenser and prime with the Assay Buffer. Add 50 ml Assay Buffer and incubate at room temperature 5 min. Empty the dispenser and prime with the Reaction Buffer (see the table below). Add 50 ul Reaction Buffer and incubate at room temperature for 20 minutes. Since the intensity of the chemiluminescent signal is time dependent, and it takes about 10 minutes to read 5 plates on luminometer, one should treat 5 plates at
10 each time and start the second set 10 minutes later.

Read the relative light unit in the luminometer. Set H12 as blank, and print the results. An increase in chemiluminescence indicates reporter activity.

Reaction Buffer Formulation:

15

| # of plates | Rxn buffer diluent (ml) | CSPD (ml) |
|-------------|-------------------------|-----------|
| 10 | 60 | 3 |
| 11 | 65 | 3.25 |
| 12 | 70 | 3.5 |
| 13 | 75 | 3.75 |
| 14 | 80 | 4 |
| 15 | 85 | 4.25 |
| 16 | 90 | 4.5 |
| 17 | 95 | 4.75 |
| 18 | 100 | 5 |
| 19 | 105 | 5.25 |
| 20 | 110 | 5.5 |
| 21 | 115 | 5.75 |
| 22 | 120 | 6 |
| 23 | 125 | 6.25 |

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| | | |
|----|-----|-------|
| 24 | 130 | 6.5 |
| 25 | 135 | 6.75 |
| 26 | 140 | 7 |
| 27 | 145 | 7.25 |
| 28 | 150 | 7.5 |
| 29 | 155 | 7.75 |
| 30 | 160 | 8 |
| 31 | 165 | 8.25 |
| 32 | 170 | 8.5 |
| 33 | 175 | 8.75 |
| 34 | 180 | 9 |
| 35 | 185 | 9.25 |
| 36 | 190 | 9.5 |
| 37 | 195 | 9.75 |
| 38 | 200 | 10 |
| 39 | 205 | 10.25 |
| 40 | 210 | 10.5 |
| 41 | 215 | 10.75 |
| 42 | 220 | 11 |
| 43 | 225 | 11.25 |
| 44 | 230 | 11.5 |
| 45 | 235 | 11.75 |
| 46 | 240 | 12 |
| 47 | 245 | 12.25 |
| 48 | 250 | 12.5 |
| 49 | 255 | 12.75 |
| 50 | 260 | 13 |

Example 38: High-Throughput Screening Assay Identifying Changes in Small Molecule Concentration and Membrane Permeability

Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium, sodium, and pH, as well as alter membrane potential. These alterations can be measured in an assay to identify supernatants which bind to receptors of a particular cell. Although the following protocol describes an assay for calcium, this protocol can easily be modified to detect changes in potassium, sodium, pH, membrane potential, or any other small molecule which is detectable by a fluorescent probe.

The following assay uses Fluorometric Imaging Plate Reader ("FLIPR") to measure changes in fluorescent molecules (Molecular Probes) that bind small molecules. Clearly, any fluorescent molecule detecting a small molecule can be used instead of the calcium fluorescent molecule, fluo-4 (Molecular Probes, Inc.; catalog no. F-14202), used here.

For adherent cells, seed the cells at 10,000 -20,000 cells/well in a Co-star black 96-well plate with clear bottom. The plate is incubated in a CO₂ incubator for 20 hours. The adherent cells are washed two times in Biotek washer with 200 ul of HBSS (Hank's Balanced Salt Solution) leaving 100 ul of buffer after the final wash.

A stock solution of 1 mg/ml fluo-4 is made in 10% pluronic acid DMSO. To load the cells with fluo-4, 50 ul of 12 ug/ml fluo-4 is added to each well. The plate is incubated at 37 degrees C in a CO₂ incubator for 60 min. The plate is washed four times in the Biotek washer with HBSS leaving 100 ul of buffer.

For non-adherent cells, the cells are spun down from culture media. Cells are re-suspended to 2.5×10^6 cells/ml with HBSS in a 50-ml conical tube. 4 ul of 1 mg/ml fluo-4 solution in 10% pluronic acid DMSO is added to each ml of cell suspension. The tube is then placed in a 37 degrees C water bath for 30-60 min. The cells are washed twice with HBSS, resuspended to 1×10^6 cells/ml, and dispensed into a microplate, 100 ul/well. The plate is centrifuged at 1000 rpm for 5 min. The plate is then washed once in Denley Cell Wash with 200 ul, followed by an aspiration step to 100 ul final volume.

For a non-cell based assay, each well contains a fluorescent molecule, such as

fluo-4 . The supernatant is added to the well, and a change in fluorescence is detected.

To measure the fluorescence of intracellular calcium, the FLIPR is set for the following parameters: (1) System gain is 300-800 mW; (2) Exposure time is 0.4 second; (3) Camera F/stop is F/2; (4) Excitation is 488 nm; (5) Emission is 530 nm; and (6) Sample addition is 50 ul. Increased emission at 530 nm indicates an extracellular signaling event caused by the a molecule, either polypeptide of the present invention or a molecule induced by polypeptide of the present invention, which has resulted in an increase in the intracellular Ca^{++} concentration.

10

Example 40: High-Throughput Screening Assay Identifying Tyrosine Kinase Activity

The Protein Tyrosine Kinases (PTK) represent a diverse group of transmembrane and cytoplasmic kinases. Within the Receptor Protein Tyrosine Kinase (RPTK) group are receptors for a range of mitogenic and metabolic growth factors including the PDGF, FGF, EGF, NGF, HGF and Insulin receptor subfamilies. In addition there are a large family of RPTKs for which the corresponding ligand is unknown. Ligands for RPTKs include mainly secreted small proteins, but also membrane-bound and extracellular matrix proteins.

Activation of RPTK by ligands involves ligand-mediated receptor dimerization, resulting in transphosphorylation of the receptor subunits and activation of the cytoplasmic tyrosine kinases. The cytoplasmic tyrosine kinases include receptor associated tyrosine kinases of the src-family (e.g., src, yes, lck, lyn, fyn) and non-receptor linked and cytosolic protein tyrosine kinases, such as the Jak family, members of which mediate signal transduction triggered by the cytokine superfamily of receptors (e.g., the Interleukins, Interferons, GM-CSF, and Leptin).

Because of the wide range of known factors capable of stimulating tyrosine kinase activity, identifying whether polypeptide of the present invention or a molecule induced by polypeptide of the present invention is capable of activating tyrosine kinase signal transduction pathways is of interest. Therefore, the following protocol

30

is designed to identify such molecules capable of activating the tyrosine kinase signal transduction pathways.

Seed target cells (e.g., primary keratinocytes) at a density of approximately 25,000 cells per well in a 96 well Loprodyne Silent Screen Plates purchased from Nalge Nunc (Naperville, IL). The plates are sterilized with two 30 minute rinses with 100% ethanol, rinsed with water and dried overnight. Some plates are coated for 2 hr with 100 ml of cell culture grade type I collagen (50 mg/ml), gelatin (2%) or polylysine (50 mg/ml), all of which can be purchased from Sigma Chemicals (St. Louis, MO) or 10% Matrigel purchased from Becton Dickinson (Bedford, MA), or calf serum, rinsed with PBS and stored at 4 degree C. Cell growth on these plates is assayed by seeding 5,000 cells/well in growth medium and indirect quantitation of cell number through use of alamarBlue as described by the manufacturer Alamar Biosciences, Inc. (Sacramento, CA) after 48 hr. Falcon plate covers #3071 from Becton Dickinson (Bedford, MA) are used to cover the Loprodyne Silent Screen Plates. Falcon Microtest III cell culture plates can also be used in some proliferation experiments.

To prepare extracts, A431 cells are seeded onto the nylon membranes of Loprodyne plates (20,000/200ml/well) and cultured overnight in complete medium. Cells are quiesced by incubation in serum-free basal medium for 24 hr. After 5-20 minutes treatment with EGF (60ng/ml) or 50 ul of the supernatant produced in Example 31, the medium was removed and 100 ml of extraction buffer ((20 mM HEPES pH 7.5, 0.15 M NaCl, 1% Triton X-100, 0.1% SDS, 2 mM Na₃VO₄, 2 mM Na₄P₂O₇ and a cocktail of protease inhibitors (# 1836170) obtained from Boehringer Mannheim (Indianapolis, IN) is added to each well and the plate is shaken on a rotating shaker for 5 minutes at 4°C. The plate is then placed in a vacuum transfer manifold and the extract filtered through the 0.45 mm membrane bottoms of each well using house vacuum. Extracts are collected in a 96-well catch/assay plate in the bottom of the vacuum manifold and immediately placed on ice. To obtain extracts clarified by centrifugation, the content of each well, after detergent solubilization for 5 minutes, is removed and centrifuged for 15 minutes at 4

degree C at 16,000 x g.

Test the filtered extracts for levels of tyrosine kinase activity. Although many methods of detecting tyrosine kinase activity are known, one method is described here.

5 Generally, the tyrosine kinase activity of a supernatant is evaluated by determining its ability to phosphorylate a tyrosine residue on a specific substrate (a biotinylated peptide). Biotinylated peptides that can be used for this purpose include PSK1 (corresponding to amino acids 6-20 of the cell division kinase cdc2-p34) and PSK2 (corresponding to amino acids 1-17 of gastrin). Both peptides are substrates for
10 a range of tyrosine kinases and are available from Boehringer Mannheim.

 The tyrosine kinase reaction is set up by adding the following components in order. First, add 10ul of 5uM Biotinylated Peptide, then 10ul ATP/Mg₂⁺ (5mM ATP/50mM MgCl₂), then 10ul of 5x Assay Buffer (40mM imidazole hydrochloride, pH7.3, 40 mM beta-glycerophosphate, 1mM EGTA, 100mM MgCl₂, 5 mM MnCl₂,
15 0.5 mg/ml BSA), then 5ul of Sodium Vanadate(1mM), and then 5ul of water. Mix the components gently and preincubate the reaction mix at 30 degree C for 2 min. Initial the reaction by adding 10ul of the control enzyme or the filtered supernatant.

 The tyrosine kinase assay reaction is then terminated by adding 10 ul of 120mM EDTA and place the reactions on ice.

20 Tyrosine kinase activity is determined by transferring 50 ul aliquot of reaction mixture to a microtiter plate (MTP) module and incubating at 37 degree C for 20 min. This allows the streptavidin coated 96 well plate to associate with the biotinylated peptide. Wash the MTP module with 300ul/well of PBS four times. Next add 75 ul of anti-phosphotyrosine antibody conjugated to horse radish peroxidase(anti-P-Tyr-
25 POD(0.5u/ml)) to each well and incubate at 37 degree C for one hour. Wash the well as above.

 Next add 100ul of peroxidase substrate solution (Boehringer Mannheim) and incubate at room temperature for at least 5 mins (up to 30 min). Measure the absorbance of the sample at 405 nm by using ELISA reader. The level of bound
30 peroxidase activity is quantitated using an ELISA reader and reflects the level of

tyrosine kinase activity.

Example 41: High-Throughput Screening Assay Identifying Phosphorylation Activity

5 As a potential alternative and/or compliment to the assay of protein tyrosine kinase activity described in Example 40, an assay which detects activation (phosphorylation) of major intracellular signal transduction intermediates can also be used. For example, as described below one particular assay can detect tyrosine phosphorylation of the Erk-1 and Erk-2 kinases. However, phosphorylation of other
10 molecules, such as Raf, JNK, p38 MAP, Map kinase kinase (MEK), MEK kinase, Src, Muscle specific kinase (MuSK), IRAK, Tec, and Janus, as well as any other phosphoserine, phosphotyrosine, or phosphothreonine molecule, can be detected by substituting these molecules for Erk-1 or Erk-2 in the following assay.

Specifically, assay plates are made by coating the wells of a 96-well ELISA
15 plate with 0.1ml of protein G (1ug/ml) for 2 hr at room temp, (RT). The plates are then rinsed with PBS and blocked with 3% BSA/PBS for 1 hr at RT. The protein G plates are then treated with 2 commercial monoclonal antibodies (100ng/well) against Erk-1 and Erk-2 (1 hr at RT) (Santa Cruz Biotechnology). (To detect other
20 molecules, this step can easily be modified by substituting a monoclonal antibody detecting any of the above described molecules.) After 3-5 rinses with PBS, the plates are stored at 4 degree C until use.

A431 cells are seeded at 20,000/well in a 96-well Loprodyne filterplate and cultured overnight in growth medium. The cells are then starved for 48 hr in basal medium (DMEM) and then treated with EGF (6ng/well) or 50 ul of the supernatants
25 obtained in Example 31 for 5-20 minutes. The cells are then solubilized and extracts filtered directly into the assay plate.

After incubation with the extract for 1 hr at RT, the wells are again rinsed. As a positive control, a commercial preparation of MAP kinase (10ng/well) is used in place of A431 extract. Plates are then treated with a commercial polyclonal (rabbit)
30 antibody (1ug/ml) which specifically recognizes the phosphorylated epitope of the

Erk-1 and Erk-2 kinases (1 hr at RT). This antibody is biotinylated by standard procedures. The bound polyclonal antibody is then quantitated by successive incubations with Europium-streptavidin and Europium fluorescence enhancing reagent in the Wallac DELFIA instrument (time-resolved fluorescence). An increased
5 fluorescent signal over background indicates a phosphorylation by polypeptide of the present invention or a molecule induced by polypeptide of the present invention.

Example 42: Assay for the Stimulation of Bone Marrow CD34+ Cell Proliferation

10 This assay is based on the ability of human CD34+ to proliferate in the presence of hematopoietic growth factors and evaluates the ability of isolated polypeptides expressed in mammalian cells to stimulate proliferation of CD34+ cells.

It has been previously shown that most mature precursors will respond to only a single signal. More immature precursors require at least two signals to respond.
15 Therefore, to test the effect of polypeptides on hematopoietic activity of a wide range of progenitor cells, the assay contains a given polypeptide in the presence or absence of other hematopoietic growth factors. Isolated cells are cultured for 5 days in the presence of Stem Cell Factor (SCF) in combination with tested sample. SCF alone has a very limited effect on the proliferation of bone marrow (BM) cells, acting in
20 such conditions only as a "survival" factor. However, combined with any factor exhibiting stimulatory effect on these cells (e.g., IL-3), SCF will cause a synergistic effect. Therefore, if the tested polypeptide has a stimulatory effect on a hematopoietic progenitors, such activity can be easily detected. Since normal BM cells have a low level of cycling cells, it is likely that any inhibitory effect of a given polypeptide, or
25 agonists or antagonists thereof, might not be detected. Accordingly, assays for an inhibitory effect on progenitors is preferably tested in cells that are first subjected to *in vitro* stimulation with SCF+IL+3, and then contacted with the compound that is being evaluated for inhibition of such induced proliferation.

Briefly, CD34+ cells are isolated using methods known in the art. The cells
30 are thawed and resuspended in medium (QBSF 60 serum-free medium with 1% L-

glutamine (500ml) Quality Biological, Inc., Gaithersburg, MD Cat# 160-204-101). After several gentle centrifugation steps at 200 x g, cells are allowed to rest for one hour. The cell count is adjusted to 2.5×10^5 cells/ml. During this time, 100 μ l of sterile water is added to the peripheral wells of a 96-well plate. The cytokines that
5 can be tested with a given polypeptide in this assay is rhSCF (R&D Systems, Minneapolis, MN, Cat# 255-SC) at 50 ng/ml alone and in combination with rhSCF and rhIL-3 (R&D Systems, Minneapolis, MN, Cat# 203-ML) at 30 ng/ml. After one hour, 10 μ l of prepared cytokines, 50 μ l of the supernatants prepared in Example 31 (supernatants at 1:2 dilution = 50 μ l) and 20 μ l of diluted cells are added to the media
10 which is already present in the wells to allow for a final total volume of 100 μ l. The plates are then placed in a 37°C/5% CO₂ incubator for five days.

Eighteen hours before the assay is harvested, 0.5 μ Ci/well of [3H] Thymidine is added in a 10 μ l volume to each well to determine the proliferation rate. The experiment is terminated by harvesting the cells from each 96-well plate to a filtermat
15 using the Tomtec Harvester 96. After harvesting, the filtermats are dried, trimmed and placed into OmniFilter assemblies consisting of one OmniFilter plate and one OmniFilter Tray. 60 μ l Microscint is added to each well and the plate sealed with TopSeal-A press-on sealing film. A bar code 15 sticker is affixed to the first plate for counting. The sealed plates is then loaded and the level of radioactivity determined
20 via the Packard Top Count and the printed data collected for analysis. The level of radioactivity reflects the amount of cell proliferation.

The studies described in this example test the activity of a given polypeptide to stimulate bone marrow CD34+ cell proliferation. One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene
25 therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof. As a nonlimiting example, potential antagonists tested in this assay would be expected to inhibit cell proliferation in the presence of cytokines and/or to increase the inhibition of cell proliferation in the presence of cytokines and a given polypeptide. In contrast, potential agonists tested in this assay would be expected to enhance cell
30 proliferation and/or to decrease the inhibition of cell proliferation in the presence of

cytokines and a given polypeptide.

The ability of a gene to stimulate the proliferation of bone marrow CD34+ cells indicates that polynucleotides and polypeptides corresponding to the gene are useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein.

Example 43: Assay for Extracellular Matrix Enhanced Cell Response (EMECCR)

The objective of the Extracellular Matrix Enhanced Cell Response (EMECCR) assay is to identify gene products (e.g., isolated polypeptides) that act on the hematopoietic stem cells in the context of the extracellular matrix (ECM) induced signal.

Cells respond to the regulatory factors in the context of signal(s) received from the surrounding microenvironment. For example, fibroblasts, and endothelial and epithelial stem cells fail to replicate in the absence of signals from the ECM. Hematopoietic stem cells can undergo self-renewal in the bone marrow, but not in *in vitro* suspension culture. The ability of stem cells to undergo self-renewal *in vitro* is dependent upon their interaction with the stromal cells and the ECM protein fibronectin (fn). Adhesion of cells to fn is mediated by the $\alpha_5\beta_1$ and $\alpha_4\beta_1$ integrin receptors, which are expressed by human and mouse hematopoietic stem cells. The factor(s) which integrate with the ECM environment and responsible for stimulating stem cell self-renewal has not yet been identified. Discovery of such factors should be of great interest in gene therapy and bone marrow transplant applications

Briefly, polystyrene, non tissue culture treated, 96-well plates are coated with fn fragment at a coating concentration of $0.2 \mu\text{g}/\text{cm}^2$. Mouse bone marrow cells are plated (1,000 cells/well) in 0.2 ml of serum-free medium. Cells cultured in the presence of IL-3 (5 ng/ml) + SCF (50 ng/ml) would serve as the positive control, conditions under which little self-renewal but pronounced differentiation of the stem

cells is to be expected. Gene products of the invention (e.g., including, but not limited to, polynucleotides and polypeptides of the present invention, and supernatants produced in Example 31), are tested with appropriate negative controls in the presence and absence of SCF(5.0 ng/ml), where test factor supernates represent 10% of the total assay volume. The plated cells are then allowed to grow by incubating in a low oxygen environment (5% CO₂, 7% O₂, and 88% N₂) tissue culture incubator for 7 days. The number of proliferating cells within the wells is then quantitated by measuring thymidine incorporation into cellular DNA. Verification of the positive hits in the assay will require phenotypic characterization of the cells, which can be accomplished by scaling up of the culture system and using appropriate antibody reagents against cell surface antigens and FACScan.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

If a particular polypeptide of the present invention is found to be a stimulator of hematopoietic progenitors, polynucleotides and polypeptides corresponding to the gene encoding said polypeptide may be useful for the diagnosis and treatment of disorders affecting the immune system and hematopoiesis. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections above, and elsewhere herein. The gene product may also be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types.

Additionally, the polynucleotides and/or polypeptides of the gene of interest and/or agonists and/or antagonists thereof, may also be employed to inhibit the proliferation and differentiation of hematopoietic cells and therefore may be employed to protect bone marrow stem cells from chemotherapeutic agents during chemotherapy. This antiproliferative effect may allow administration of higher doses of chemotherapeutic agents and, therefore, more effective chemotherapeutic treatment.

Moreover, polynucleotides and polypeptides corresponding to the gene of

interest may also be useful for the treatment and diagnosis of hematopoietic related disorders such as, for example, anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia.

Example 44: Human Dermal Fibroblast and Aortic Smooth Muscle Cell Proliferation

10 The polypeptide of interest is added to cultures of normal human dermal fibroblasts (NHDF) and human aortic smooth muscle cells (AoSMC) and two co-assays are performed with each sample. The first assay examines the effect of the polypeptide of interest on the proliferation of normal human dermal fibroblasts (NHDF) or aortic smooth muscle cells (AoSMC). Aberrant growth of fibroblasts or
15 smooth muscle cells is a part of several pathological processes, including fibrosis, and restenosis. The second assay examines IL6 production by both NHDF and SMC. IL6 production is an indication of functional activation. Activated cells will have increased production of a number of cytokines and other factors, which can result in a proinflammatory or immunomodulatory outcome. Assays are run with and without
20 co-TNF α stimulation, in order to check for costimulatory or inhibitory activity.

Briefly, on day 1, 96-well black plates are set up with 1000 cells/well (NHDF) or 2000 cells/well (AoSMC) in 100 μ l culture media. NHDF culture media contains: Clonetics FB basal media, 1mg/ml hFGF, 5mg/ml insulin, 50mg/ml gentamycin, 2%FBS, while AoSMC culture media contains Clonetics SM basal media, 0.5 μ g/ml
25 hEGF, 5mg/ml insulin, 1 μ g/ml hFGF, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B, 5%FBS. After incubation at 37°C for at least 4-5 hours, culture media is aspirated and replaced with growth arrest media. Growth arrest media for NHDF contains fibroblast basal media, 50mg/ml gentamycin, 2% FBS, while growth arrest media for AoSMC contains SM basal media, 50mg/ml gentamycin, 50 μ g/ml Amphotericin B,
30 0.4% FBS. Incubate at 37°C until day 2.

On day 2, serial dilutions and templates of the polypeptide of interest are designed such that they always include media controls and known-protein controls. For both stimulation and inhibition experiments, proteins are diluted in growth arrest media. For inhibition experiments, TNFa is added to a final concentration of 2ng/ml (NHDF) or 5ng/ml (AoSMC). Add 1/3 vol media containing controls or polypeptides of the present invention and incubate at 37°C/5% CO₂ until day 5.

Transfer 60µl from each well to another labeled 96-well plate, cover with a plate-sealer, and store at 4°C until Day 6 (for IL6 ELISA). To the remaining 100 µl in the cell culture plate, aseptically add Alamar Blue in an amount equal to 10% of the culture volume (10µl). Return plates to incubator for 3 to 4 hours. Then measure fluorescence with excitation at 530nm and emission at 590nm using the CytoFluor. This yields the growth stimulation/inhibition data.

On day 5, the IL6 ELISA is performed by coating a 96 well plate with 50-100 µl/well of Anti-Human IL6 Monoclonal antibody diluted in PBS, pH 7.4, incubate ON at room temperature.

On day 6, empty the plates into the sink and blot on paper towels. Prepare Assay Buffer containing PBS with 4% BSA. Block the plates with 200 µl/well of Pierce Super Block blocking buffer in PBS for 1-2 hr and then wash plates with wash buffer (PBS, 0.05% Tween-20). Blot plates on paper towels. Then add 50 µl/well of diluted Anti-Human IL-6 Monoclonal, Biotin-labeled antibody at 0.50 mg/ml. Make dilutions of IL-6 stock in media (30, 10, 3, 1, 0.3, 0 ng/ml). Add duplicate samples to top row of plate. Cover the plates and incubate for 2 hours at RT on shaker. Plates are washed with wash buffer and blotted on paper towels. Dilute EU-labeled Streptavidin 1:1000 in Assay buffer, and add 100 µl/well. Cover the plate and incubate 1 h at RT. Plates are again washed with wash buffer and blotted on paper towels. Add 100 µl/well of Enhancement Solution and shake for 5 minutes. Read the plate on the Wallac DELFIA Fluorometer. Readings from triplicate samples in each assay are tabulated and averaged.

A positive result in this assay suggests AoSMC cell proliferation and that the polypeptide of the present invention may be involved in dermal fibroblast

proliferation and/or smooth muscle cell proliferation. A positive result also suggests many potential uses of polypeptides, polynucleotides, agonists and/or antagonists of the polynucleotide/polypeptide of the present invention which gives a positive result. For example, inflammation and immune responses, wound healing, and angiogenesis, as detailed throughout this specification. Particularly, polypeptides of the present invention and polynucleotides of the present invention may be used in wound healing and dermal regeneration, as well as the promotion of vasculogenesis, both of the blood vessels and lymphatics. The growth of vessels can be used in the treatment of, for example, cardiovascular diseases. Additionally, antagonists of polypeptides and polynucleotides of the invention may be useful in treating diseases, disorders, and/or conditions which involve angiogenesis by acting as an anti-vascular (e.g., anti-angiogenesis). These diseases, disorders, and/or conditions are known in the art and/or are described herein, such as, for example, malignancies, solid tumors, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis. Moreover, antagonists of polypeptides and polynucleotides of the invention may be useful in treating anti-hyperproliferative diseases and/or anti-inflammatory known in the art and/or described herein.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

Example 45: Cellular Adhesion Molecule (CAM) Expression on Endothelial Cells

5 The recruitment of lymphocytes to areas of inflammation and angiogenesis involves specific receptor-ligand interactions between cell surface adhesion molecules (CAMs) on lymphocytes and the vascular endothelium. The adhesion process, in both normal and pathological settings, follows a multi-step cascade that involves intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1
10 (VCAM-1), and endothelial leukocyte adhesion molecule-1 (E-selectin) expression on endothelial cells (EC). The expression of these molecules and others on the vascular endothelium determines the efficiency with which leukocytes may adhere to the local vasculature and extravasate into the local tissue during the development of an inflammatory response. The local concentration of cytokines and growth factor
15 participate in the modulation of the expression of these CAMs.

Briefly, endothelial cells (e.g., Human Umbilical Vein Endothelial cells (HUVECs)) are grown in a standard 96 well plate to confluence, growth medium is removed from the cells and replaced with 100 µl of 199 Medium (10% fetal bovine serum (FBS)). Samples for testing and positive or negative controls are added to the
20 plate in triplicate (in 10 µl volumes). Plates are then incubated at 37°C for either 5 h (selectin and integrin expression) or 24 h (integrin expression only). Plates are aspirated to remove medium and 100 µl of 0.1% paraformaldehyde-PBS(with Ca++ and Mg++) is added to each well. Plates are held at 4°C for 30 min. Fixative is removed from the wells and wells are washed 1X with PBS(+Ca,Mg) + 0.5% BSA
25 and drained. 10 µl of diluted primary antibody is added to the test and control wells. Anti-ICAM-1-Biotin, Anti-VCAM-1-Biotin and Anti-E-selectin-Biotin are used at a concentration of 10 µg/ml (1:10 dilution of 0.1 mg/ml stock antibody). Cells are incubated at 37°C for 30 min. in a humidified environment. Wells are washed three times with PBS(+Ca,Mg) + 0.5% BSA. 20 µl of diluted ExtrAvidin-Alkaline
30 Phosphatase (1:5,000 dilution, referred to herein as the working dilution) are added to

each well and incubated at 37°C for 30 min. Wells are washed three times with PBS(+Ca,Mg)+0.5% BSA. Dissolve 1 tablet of p-Nitrophenol Phosphate pNPP per 5 ml of glycine buffer (pH 10.4). 100 µl of pNPP substrate in glycine buffer is added to each test well. Standard wells in triplicate are prepared from the working dilution of the ExtrAvidin-Alkaline Phosphatase in glycine buffer: 1:5,000 (10^0) > $10^{-0.5}$ > 10^{-1} > $10^{-1.5}$. 5 µl of each dilution is added to triplicate wells and the resulting AP content in each well is 5.50 ng, 1.74 ng, 0.55 ng, 0.18 ng. 100 µl of pNPP reagent is then added to each of the standard wells. The plate is incubated at 37°C for 4h. A volume of 50 µl of 3M NaOH is added to all wells. The plate is read on a plate reader at 405 nm using the background subtraction option on blank wells filled with glycine buffer only. Additionally, the template is set up to indicate the concentration of AP-conjugate in each standard well [5.50 ng; 1.74 ng; 0.55 ng; 0.18 ng]. Results are indicated as amount of bound AP-conjugate in each sample.

15 *Example 46: Alamar Blue Endothelial Cells Proliferation Assay*

This assay may be used to quantitatively determine protein mediated inhibition of bFGF-induced proliferation of Bovine Lymphatic Endothelial Cells (LECs), Bovine Aortic Endothelial Cells (BAECs) or Human Microvascular Uterine Myometrial Cells (UTMECs). This assay incorporates a fluorometric growth indicator based on detection of metabolic activity. A standard Alamar Blue Proliferation Assay is prepared in EGM-2MV with 10 ng /ml of bFGF added as a source of endothelial cell stimulation. This assay may be used with a variety of endothelial cells with slight changes in growth medium and cell concentration. Dilutions of the protein batches to be tested are diluted as appropriate. Serum-free medium (GIBCO SFM) without bFGF is used as a non-stimulated control and Angiostatin or TSP-1 are included as a known inhibitory controls.

Briefly, LEC, BAECs or UTMECs are seeded in growth media at a density of 5000 to 2000 cells/well in a 96 well plate and placed at 37-C overnight. After the overnight incubation of the cells, the growth media is removed and replaced with

GIBCO EC-SFM. The cells are treated with the appropriate dilutions of the protein of interest or control protein sample(s) (prepared in SFM) in triplicate wells with additional bFGF to a concentration of 10 ng/ ml. Once the cells have been treated with the samples, the plate(s) is/are placed back in the 37° C incubator for three days.

- 5 After three days 10 ml of stock alamar blue (Biosource Cat# DAL1100) is added to each well and the plate(s) is/are placed back in the 37°C incubator for four hours. The plate(s) are then read at 530nm excitation and 590nm emission using the CytoFluor fluorescence reader. Direct output is recorded in relative fluorescence units.

- 10 Alamar blue is an oxidation-reduction indicator that both fluoresces and changes color in response to chemical reduction of growth medium resulting from cell growth. As cells grow in culture, innate metabolic activity results in a chemical reduction of the immediate surrounding environment. Reduction related to growth causes the indicator to change from oxidized (non-fluorescent blue) form to reduced (fluorescent red) form. i.e. stimulated proliferation will produce a stronger signal and
- 15 inhibited proliferation will produce a weaker signal and the total signal is proportional to the total number of cells as well as their metabolic activity. The background level of activity is observed with the starvation medium alone. This is compared to the output observed from the positive control samples (bFGF in growth medium) and protein dilutions.

20

Example 47: Detection of Inhibition of a Mixed Lymphocyte Reaction

This assay can be used to detect and evaluate inhibition of a Mixed Lymphocyte Reaction (MLR) by gene products (e.g., isolated polypeptides).

- 25 Inhibition of a MLR may be due to a direct effect on cell proliferation and viability, modulation of costimulatory molecules on interacting cells, modulation of adhesiveness between lymphocytes and accessory cells, or modulation of cytokine production by accessory cells. Multiple cells may be targeted by these polypeptides since the peripheral blood mononuclear fraction used in this assay includes T, B and

natural killer lymphocytes, as well as monocytes and dendritic cells.

Polypeptides of interest found to inhibit the MLR may find application in diseases associated with lymphocyte and monocyte activation or proliferation. These include, but are not limited to, diseases such as asthma, arthritis, diabetes, inflammatory skin conditions, psoriasis, eczema, systemic lupus erythematosus, multiple sclerosis, glomerulonephritis, inflammatory bowel disease, crohn's disease, ulcerative colitis, arteriosclerosis, cirrhosis, graft vs. host disease, host vs. graft disease, hepatitis, leukemia and lymphoma.

Briefly, PBMCs from human donors are purified by density gradient centrifugation using Lymphocyte Separation Medium (LSM[®], density 1.0770 g/ml, Organon Teknika Corporation, West Chester, PA). PBMCs from two donors are adjusted to 2×10^6 cells/ml in RPMI-1640 (Life Technologies, Grand Island, NY) supplemented with 10% FCS and 2 mM glutamine. PBMCs from a third donor is adjusted to 2×10^5 cells/ml. Fifty microliters of PBMCs from each donor is added to wells of a 96-well round bottom microtiter plate. Dilutions of test materials (50 μ l) is added in triplicate to microtiter wells. Test samples (of the protein of interest) are added for final dilution of 1:4; rhIL-2 (R&D Systems, Minneapolis, MN, catalog number 202-IL) is added to a final concentration of 1 μ g/ml; anti-CD4 mAb (R&D Systems, clone 34930.11, catalog number MAB379) is added to a final concentration of 10 μ g/ml. Cells are cultured for 7-8 days at 37°C in 5% CO₂, and 1 μ C of [³H] thymidine is added to wells for the last 16 hrs of culture. Cells are harvested and thymidine incorporation determined using a Packard TopCount. Data is expressed as the mean and standard deviation of triplicate determinations.

Samples of the protein of interest are screened in separate experiments and compared to the negative control treatment, anti-CD4 mAb, which inhibits proliferation of lymphocytes and the positive control treatment, IL-2 (either as recombinant material or supernatant), which enhances proliferation of lymphocytes.

One skilled in the art could easily modify the exemplified studies to test the activity of polynucleotides (e.g., gene therapy), antibodies, agonists, and/or antagonists and fragments and variants thereof.

It will be clear that the invention may be practiced otherwise than as particularly described in the foregoing description and examples. Numerous modifications and variations of the present invention are possible in light of the above teachings and, therefore, are within the scope of the appended claims.

5 The entire disclosure of each document cited (including patents, patent applications, journal articles, abstracts, laboratory manuals, books, or other disclosures) in the Background of the Invention, Detailed Description, and Examples is hereby incorporated herein by reference. Further, the hard copy of the sequence listing submitted herewith and the corresponding computer readable form are both
10 incorporated herein by reference in their entireties. Moreover, the hard copy of and the corresponding computer readable form of the Sequence Listing of Serial No. 60/124,270 are also incorporated herein by reference in their entireties.

| | | |
|---|-----------------|-------------------------------|
| Applicant's or agent's file reference number | 411 PA103PCT | International application no. |
|---|-----------------|-------------------------------|

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

| | |
|---|-----------------------------------|
| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT | |
| Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <u>American Type Culture Collection</u> | |
| Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u> | |
| Date of deposit <u>20 May 1997</u> | Accession Number <u>209059</u> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) | |
| This information is continued on an additional sheet <input type="checkbox"/> | |
| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |

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| <input checked="" type="checkbox"/> This sheet was received with the international application | <input type="checkbox"/> This sheet was received by the International Bureau on: |
| RO/US 08 MAR 2000 | |
| Authorized officer <u>Tonia Harrod</u> <u>PCT/Internat'l Appl Processing Div.</u> <u>(703) 305-3670</u> | Authorized officer |

ATCC Deposit No. 209059**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 209059

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <u>American Type Culture Collection</u> | |
| Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u> | |
| Date of deposit <u>20 May 1997</u> | Accession Number <u>209060</u> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. 209060**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209060

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| Applicant's or agent's file reference number | PA103PCT | International application N |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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|---|-----------------------------------|
| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <u>American Type Culture Collection</u> | |
| Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u> | |
| Date of deposit <u>20 May 1997</u> | Accession Number <u>209061</u> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. 209061

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 209061

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 20 May 1997 | Accession Number 209062 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |

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ATCC Deposit No. 209062**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 209062

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| Applicant's or agent's file reference number | PA103PCT | International application i |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <u>American Type Culture Collection</u> | |
| Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2209</u> <u>United States of America</u> | |
| Date of deposit <u>20 May 1997</u> | Accession Number <u>209063</u> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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| RO/US 26 MAR 2000 | |
| Authorized officer <u>Yolanda Harrod</u> PCT/Internat'l Appl Processing Div. (703) 305-3670 | Authorized officer |

ATCC Deposit No. 209063

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

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Page 2
ATCC Deposit No. 209063

DENMARK

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SWEDEN

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NETHERLANDS

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 20 May 1997 | Accession Number 209064 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. 209064**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

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ATCC Deposit No. 209064

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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|---|-----------------|---------------------------|
| Applicant's or agent's file reference number | 429 PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <u>American Type Culture Collection</u> | |
| Address of depositary institution (including postal code and country) <u>10801 University Boulevard</u> <u>Manassas, Virginia 20110-2709</u> <u>United States of America</u> | |
| Date of deposit <u>20 May 1997</u> | Accession Number <u>209065</u> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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| <input checked="" type="checkbox"/> For receiving Office use only This sheet was received with the international application RO/US 05 MAR 2000 | <input type="checkbox"/> For International Bureau use only This sheet was received by the International Bureau on: |
| Authorized officer <u>Isabella Harroo</u> <u>PCT/Internat'l Appl Processing Div.</u> <u>(703) 305-3870</u> | Authorized officer |

ATCC Deposit No. 209065

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 209065

DENMARK

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SWEDEN

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NETHERLANDS

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p> | |
| Address of depositary institution (including postal code and country) <p style="text-align: center;">10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p> | |
| Date of deposit <p style="text-align: center;">20 May 1997</p> | Accession Number <p style="text-align: center;">209066</p> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
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| <p>For receiving Office use only</p> <p><input checked="" type="checkbox"/> This sheet was received with the international application</p> <p style="text-align: center;">RO/US 03 MAR 2000</p> <p>Authorized officer: Y. H. Harrod PCT/Int'l Appl Processing Div. (703) 305-3070</p> | <p>For International Bureau use only</p> <p><input type="checkbox"/> This sheet was received by the International Bureau on:</p> <p>Authorized officer:</p> |
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ATCC Deposit No. 209066**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2
ATCC Deposit No. 209066

DENMARK

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SWEDEN

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NETHERLANDS

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|---|-----------------|---------------------------|
| Applicant's or agent's file reference number | 435 PA103PCT | International application |
|---|-----------------|---------------------------|

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 20 May 1997 | Accession Number 209067 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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| <input checked="" type="checkbox"/> This sheet was received with the international application | <input type="checkbox"/> This sheet was received by the International Bureau on: |
| RO/US 03 MAR 2000 | |
| Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. | Authorized officer |

ATCC Deposit No. 209067

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. 209067

DENMARK

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SWEDEN

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NETHERLANDS

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438

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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|---|-----------------------------------|
| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT | |
| Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <p>American Type Culture Collection</p> | |
| Address of depositary institution (including postal code and country) <p>10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p> | |
| Date of deposit <p>20 May 1997</p> | Accession Number <p>209068</p> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) | |
| This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
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| <input checked="" type="checkbox"/> This sheet was received with the international application | <input type="checkbox"/> This sheet was received by the International Bureau on: |
| Authorized officer <p>Yolanda Harrod PCT/Internat'l Appl Processing Div. 0031 305 3870</p> | Authorized officer |

ATCC Deposit No. 209068

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. 209068

DENMARK

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NETHERLANDS

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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|---|-----------------------------------|
| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 20 May 1997 | Accession Number 209069 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
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| For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application ROUS 03 MAR 2000 Authorized officer Patricia Harrod PCT/Int'l App Processing Div. (703) 305-3870 | For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer |
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ATCC Deposit No. 209069

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

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FINLAND

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UNITED KINGDOM

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Page 2
ATCC Deposit No. 209069

DENMARK

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT | |
| Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 12 January 1998 | Accession Number 209579 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) | |
| This information is continued on an additional sheet <input type="checkbox"/> | |
| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |

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| For receiving Office use only <input checked="" type="checkbox"/> This sheet was received with the international application 20 MAR 2000 Authorized officer [Signature] | For International Bureau use only <input type="checkbox"/> This sheet was received by the International Bureau on: Authorized officer |
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ATCC Deposit No. 209579

CANADA

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 209579

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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|---|-----------------------------------|
| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT | |
| Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 12 January 1998 | Accession Number 209578 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) | |
| This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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| For receiving Office use only | For International Bureau use only |
| <input checked="" type="checkbox"/> This sheet was received with the international application | <input type="checkbox"/> This sheet was received by the International Bureau on: |
| RO/US 03 MAR 2000 | |
| Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. | Authorized officer |

ATCC Deposit No. 209578**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 209578

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> . line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p> | |
| Address of depositary institution (including postal code and country) <p style="text-align: center;">10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p> | |
| Date of deposit <p style="text-align: center;">16 July 1998</p> | Accession Number <p style="text-align: center;">203067</p> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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| Authorized officer: Janita Harrod |
| PCT/Int'l Appl Processing Div. |
| 7034 305-3679 |

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ATCC Deposit No. 203067**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 203067

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| 453 | |
| Applicant's or agent's file reference number | PA103PCT |
| International application | |

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 16 July 1998 | Accession Number 203068 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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| RO/US 03 MAR 2000 | |
| Authorized officer Yolanda Harrod PCT/Internat'l Appl Processing Div. | Authorized officer |

ATCC Deposit No. 203068**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

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FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2
ATCC Deposit No. 203068

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| 456 | |
| Applicant's or agent's file reference number | PA103PCT |
| International application? | |

INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page 72, line N/A | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 1 February 1999 | Accession Number 203609 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |

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ATCC Deposit No. 203609**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203609

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

The applicant hereby requests that, until the application has been laid open to public inspection (by the Swedish Patent Office), or has been finally decided upon by the Swedish Patent Office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the International Bureau before the expiration of 16 months from the priority date (preferably on the Form PCT/RO/134 reproduced in annex Z of Volume I of the PCT Applicant's Guide). If such a request has been filed by the applicant any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Swedish Patent Office or any person approved by a applicant in the individual case.

NETHERLANDS

The applicant hereby requests that until the date of a grant of a Netherlands patent or until the date on which the application is refused or withdrawn or lapsed, the microorganism shall be made available as provided in the 31F(1) of the Patent Rules only by the issue of a sample to an expert. The request to this effect must be furnished by the applicant with the Netherlands Industrial Property Office before the date on which the application is made available to the public under Section 22C or Section 25 of the Patents Act of the Kingdom of the Netherlands, whichever of the two dates occurs earlier.

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| Applicant's or agent's file reference number | PA103PCT | International application |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p> | |
| Address of depositary institution (including postal code and country) <p style="text-align: center;">10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p> | |
| Date of deposit <p style="text-align: center;">1 February 1999</p> | Accession Number <p style="text-align: center;">203610</p> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. 203610**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

The applicant hereby requests that the application has been laid open to public inspection (by the Norwegian Patent Office), or has been finally decided upon by the Norwegian Patent Office without having been laid open inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Norwegian Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Norwegian Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on the list of recognized experts drawn up by the Norwegian Patent Office or any person approved by the applicant in the individual case.

AUSTRALIA

The applicant hereby gives notice that the furnishing of a sample of a microorganism shall only be effected prior to the grant of a patent, or prior to the lapsing, refusal or withdrawal of the application, to a person who is a skilled addressee without an interest in the invention (Regulation 3.25(3) of the Australian Patents Regulations).

FINLAND

The applicant hereby requests that, until the application has been laid open to public inspection (by the National Board of Patents and Regulations), or has been finally decided upon by the National Board of Patents and Registration without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art.

UNITED KINGDOM

The applicant hereby requests that the furnishing of a sample of a microorganism shall only be made available to an expert. The request to this effect must be filed by the applicant with the International Bureau before the completion of the technical preparations for the international publication of the application.

Page 2

ATCC Deposit No. 203610

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

SWEDEN

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NETHERLANDS

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| Applicant's or agent's file reference number | 462 PA103PCT | International application number |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 17 November 1998 | Accession Number 203485 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. 203485**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. 203485

DENMARK

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SWEDEN

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NETHERLANDS

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| Applicant's or agent's file reference number | PA103PCT | International application? |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 18 June 1999 | Accession Number PTA-252 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. PTA-252**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2

ATCC Deposit No. PTA-252

DENMARK

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SWEDEN

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NETHERLANDS

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| Applicant's or agent's file reference number | PA103PCT | International application No. |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution American Type Culture Collection | |
| Address of depositary institution (including postal code and country) 10801 University Boulevard Manassas, Virginia 20110-2209 United States of America | |
| Date of deposit 18 June 1999 | Accession Number PTA-253 |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. PTA-253**CANADA**

The applicant requests that, until either a Canadian patent has been issued on the basis of an application or the application has been refused, or is abandoned and no longer subject to reinstatement, or is withdrawn, the Commissioner of Patents only authorizes the furnishing of a sample of the deposited biological material referred to in the application to an independent expert nominated by the Commissioner, the applicant must, by a written statement, inform the International Bureau accordingly before completion of technical preparations for publication of the international application.

NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2
ATCC Deposit No. PTA-253

DENMARK

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SWEDEN

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NETHERLANDS

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| Applicant's or agent's file reference number | PA103PCT | International application? |
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INDICATIONS RELATING TO A DEPOSITED MICROORGANISM

(PCT Rule 13bis)

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| A. The indications made below relate to the microorganism referred to in the description on page <u>72</u> , line <u>N/A</u> | |
| B. IDENTIFICATION OF DEPOSIT Further deposits are identified on an additional sheet <input type="checkbox"/> | |
| Name of depositary institution <p style="text-align: center;">American Type Culture Collection</p> | |
| Address of depositary institution (including postal code and country) <p style="text-align: center;">10801 University Boulevard Manassas, Virginia 20110-2209 United States of America</p> | |
| Date of deposit <p style="text-align: center;">22 December 1999</p> | Accession Number <p style="text-align: center;">PTA-1081</p> |
| C. ADDITIONAL INDICATIONS (leave blank if not applicable) This information is continued on an additional sheet <input type="checkbox"/> | |
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| D. DESIGNATED STATES FOR WHICH INDICATIONS ARE MADE (if the indications are not for all designated States) | |
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| E. SEPARATE FURNISHING OF INDICATIONS (leave blank if not applicable) | |
| The indications listed below will be submitted to the International Bureau later (specify the general nature of the indications e.g., "Accession Number of Deposit") | |
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ATCC Deposit No. PTA-1081**CANADA**

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NORWAY

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AUSTRALIA

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FINLAND

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UNITED KINGDOM

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Page 2
ATCC Deposit No. PTA-1081

DENMARK

The applicant hereby requests that, until the application has been laid open to public inspection (by the Danish Patent Office), or has been finally decided upon by the Danish Patent office without having been laid open to public inspection, the furnishing of a sample shall only be effected to an expert in the art. The request to this effect shall be filed by the applicant with the Danish Patent Office not later than at the time when the application is made available to the public under Sections 22 and 33(3) of the Danish Patents Act. If such a request has been filed by the applicant, any request made by a third party for the furnishing of a sample shall indicate the expert to be used. That expert may be any person entered on a list of recognized experts drawn up by the Danish Patent Office or any person by the applicant in the individual case.

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NETHERLANDS

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What Is Claimed Is:

1. An isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence at least 95% identical to a sequence selected from the group consisting of:
- 5
- (a) a polynucleotide fragment of SEQ ID NO:X or a polynucleotide fragment of the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (b) a polynucleotide encoding a polypeptide fragment of SEQ ID NO:Y or a
10 polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (c) a polynucleotide encoding a polypeptide fragment of a polypeptide encoded by SEQ ID NO:X or a polypeptide fragment encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - 15 (d) a polynucleotide encoding a polypeptide domain of SEQ ID NO:Y or a polypeptide domain encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X;
 - (e) a polynucleotide encoding a polypeptide epitope of SEQ ID NO:Y or a polypeptide epitope encoded by the cDNA sequence included in the related cDNA
20 clone, which is hybridizable to SEQ ID NO:X;
 - (f) a polynucleotide encoding a polypeptide of SEQ ID NO:Y or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X, having biological activity;
 - (g) a polynucleotide which is a variant of SEQ ID NO:X;
 - 25 (h) a polynucleotide which is an allelic variant of SEQ ID NO:X;
 - (i) a polynucleotide which encodes a species homologue of the SEQ ID NO:Y;
 - (j) a polynucleotide capable of hybridizing under stringent conditions to any one of the polynucleotides specified in (a)-(i), wherein said polynucleotide does not
30 hybridize under stringent conditions to a nucleic acid molecule having a nucleotide

sequence of only A residues or of only T residues.

2. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding a protein.

3. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises a nucleotide sequence encoding the sequence identified as SEQ ID NO:Y or the polypeptide encoded by the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

4. The isolated nucleic acid molecule of claim 1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:X or the cDNA sequence included in the related cDNA clone, which is hybridizable to SEQ ID NO:X.

5. The isolated nucleic acid molecule of claim 2, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

6. The isolated nucleic acid molecule of claim 3, wherein the nucleotide sequence comprises sequential nucleotide deletions from either the C-terminus or the N-terminus.

7. A recombinant vector comprising the isolated nucleic acid molecule of claim 1.

8. A method of making a recombinant host cell comprising the isolated nucleic acid molecule of claim 1.

9. A recombinant host cell produced by the method of claim 8.

10. The recombinant host cell of claim 9 comprising vector sequences.
11. An isolated polypeptide comprising an amino acid sequence at least
5 95% identical to a sequence selected from the group consisting of:
- (a) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (b) a polypeptide fragment of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone, having biological activity;
 - 10 (c) a polypeptide domain of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (d) a polypeptide epitope of SEQ ID NO:Y or of the sequence encoded by the cDNA included in the related cDNA clone;
 - (e) a full length protein of SEQ ID NO:Y or of the sequence encoded by the
15 cDNA included in the related cDNA clone;
 - (f) a variant of SEQ ID NO:Y;
 - (g) an allelic variant of SEQ ID NO:Y; or
 - (h) a species homologue of the SEQ ID NO:Y.
- 20 12. The isolated polypeptide of claim 11, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.
- 25 13. An isolated antibody that binds specifically to the isolated polypeptide of claim 11.
14. A recombinant host cell that expresses the isolated polypeptide of claim 11.
- 30 15. A method of making an isolated polypeptide comprising:

(a) culturing the recombinant host cell of claim 14 under conditions such that said polypeptide is expressed; and

(b) recovering said polypeptide.

5 16. The polypeptide produced by claim 15.

17. A method for preventing, treating, or ameliorating a medical condition, comprising administering to a mammalian subject a therapeutically effective amount of the polypeptide of claim 11 or the polynucleotide of claim 1.

10

18. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

(a) determining the presence or absence of a mutation in the polynucleotide of claim 1; and

15 (b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or absence of said mutation.

19. A method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising:

20 (a) determining the presence or amount of expression of the polypeptide of claim 11 in a biological sample; and

(b) diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.

25 20. A method for identifying a binding partner to the polypeptide of claim 11 comprising:

(a) contacting the polypeptide of claim 11 with a binding partner; and

(b) determining whether the binding partner effects an activity of the polypeptide.

30

21. The gene corresponding to the cDNA sequence of SEQ ID NO:Y.
22. A method of identifying an activity in a biological assay, wherein the method comprises:
- 5 (a) expressing SEQ ID NO:X in a cell;
- (b) isolating the supernatant;
- (c) detecting an activity in a biological assay; and
- (d) identifying the protein in the supernatant having the activity.
- 10 23. The product produced by the method of claim 20.

SEQUENCE LISTING

<110> Craig Rosen,
Steve Ruben

<120> Human Breast and Ovarian Cancer Associated Gene Sequences and
Polypeptides

<130> PA103PCT

<140> Unassigned

<141> 2000-03-08

<150> 60/124,270

<151> 1999-03-12

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<210> 14

<211> 2347

<212> DNA

<213> Homo sapiens

<400> 14

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<210> 15

<211> 2006

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (862)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1006)

<223> n equals a,t,g, or c

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<210> 16

<211> 986

<212> DNA

<213> Homo sapiens

<220>

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<220>

<221> misc feature

<222> (932)

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<220>

<221> misc feature

<222> (933)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (985)

<223> n equals a,t,g, or c

<400> 16

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<210> 17

<211> 1589

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (25)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (555)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1033)

<223> n equals a,t,g, or c

<400> 17

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<210> 18

<211> 846

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (746)

<223> n equals a,t,g, or c

<400> 18

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<210> 19
<211> 2192
<212> DNA
<213> Homo sapiens

<220>
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<222> (115)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2106)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2118)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2143)
<223> n equals a,t,g, or c

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<210> 20

<211> 1011

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (54)

<223> n equals a,t,g, or c

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<210> 21

<211> 2019

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2003)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2007)

<223> n equals a,t,g, or c

<400> 21

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acccactggt ttctctctcc catggacaca gtcacagagg ctgggatggc catagcaatg 180
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cggatttggg ttcatccacc acaactgtac amctgaattc caggccaatg aagttyggaa 360
agtgaaggty wgaaggggcaa cgatcattag caagcgctcc tgggaattgc actgaggtgg 420
ggtggggtgg gagtaggggt ttattctaag ttagtattct ttcttccac catggggttc 480
agttactgag aagaccctga gattctgttt cttaaagcag cagcaataga ccagggtgac 540
agtgcctcca gcctacccat gtctctaaga tgtgttggtg tgatttggtc ttgtggcact 600
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cagaccctgt ggtcctcagc cccaaggatc gcgtgcggga tgtttttrag gccaaaggccc 780
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acccaagtcc gagccatgat gtactctggg gagcttaagt ttgagaagag aacgtcctca 1860
gcccagggtg aagggtggct ccatagcctc cattcgatg agaagcggct tttctgaaaa 1920
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aaaaaaaaat tctcgggggg ggnccngta cccaattgg 2019
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<210> 22

<211> 2022

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1588)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1615)

<223> n equals a,t,g, or c

<400> 22

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tgtgacgccca ctcaccttta ctgaggtgca cgagggccgt gctgacatca tgatcgactt 180
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gccttcttcc ccaagactca ccgagaaggg gatgtccact tcgactatga tgagacctgg 300
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gctaccactt gactctcagc ccagatgact gcaggggctt tcaacaccta tatggccagc 480
cctggccact gtcacctcca ggacccagc cctgggcccc caggctggga tagacaccaa 540
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cagccctgtg gacgtgcct tcgaggatgc ccagggccac atttggttct tccaaggtgc 780
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caggccggat cctcctgaag cccttttcgc agcactgcta tcctccaaag ccattgtaaa 1860
tgtgtgtaca gtgtgtataa acctcttctt tctttttttt ttttaaaactg aggattgtca 1920
ttaaacacag ttgttttcta aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1980
aaaaaaaaaa aaaaaggggc gccgctcgcg atctagaact ag 2022
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<210> 23

<211> 1126

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1126)

<223> n equals a,t,g, or c

<400> 23

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gtaaacgtgt gacgggggaa agccaagggtc tggagaagct ccaggaaca ayygatggcc 180
ttgcagcact cacacaggac ccccttcccc taccctctcc tctctgccgc aatacaggaa 240
ccccagggg aaagatgagc ttttctaggc tacaattttc tcccagggaag ctttgatttt 300
taccgtttct tccctgtatt ttctttctct actttgagga aaccaaagta accttttgca 360
cctgtctct tgaatgata tagccagaaa aacgtgttgc cttgaaccac ttccctcatc 420
tctctccaa gacactgttg acttggtcac cagctcctcc cttgttctct aagttccact 480
gagctccatg tgccccctct accatttgca gagtcctgca cagttttctg gctggagcct 540
agaacaggcc tccaagttt taggacaaac agctcagttc tagtctctct ggggccacac 600
agaaactctt ttggggtccc tttttctccc tctggatcaa agtaggcagg accatgggac 660
caggctcttg agctgagcct ctacctgta ctctccgaa aaatcctct cctctgaggc 720
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gttgagctgt tgcctcagtc cccaacaga tgctttctct tctctgcctc cctcaccctg 840
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gagtattggg tagatatttt ttctgaatac aaagtgatgt gtttaaatac tgcaattaaa 1080
gtgatactga aacacaaaaa aaaaaaaaaa aaaaaaaan 1126
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<210> 24

<211> 2598

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2304)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2500)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2533)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2553)

<223> n equals a,t,g, or c

<400> 24

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raggtttaa garactacca gaccattttc caatgaatgt cttggtacca ccagaccctg 120
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agttcctatt gattcatcag attttgcatt ggatattcgc atgcctgggg ttacacctaa 180
acagtccgat acatacttct gcatgtctat gcgaatacca gtggatgagg aagccttcgt 240
gattgacttc aagcctcgag ccagcatgga tactgtccat cacatgttac tttttggatg 300
caatatgcct tcatccactg graattactg gttttgtgat gaaggaaacct gtacagataa 360
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tggattcaga gttggaggag agactggaag taaatacttt gtactacagg tacactatgg 480
ggatattagt gcttttagag ataatacaa ggactgttct ggtgtgtcct tacacctcac 540
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ggaaatccaa agaagcccga gggcatttgt tgtttcccn ttacaacctc tcgggttatt 2520
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aggggccctt tgggaaga 2598

<210> 25

<211> 411

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (358)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (368)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (381)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (387)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (392)

<223> n equals a,t,g, or c

<400> 25

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cgcaccggcc caggcgcgcg gggccccgcg gctgctgttg ctgcagtc tgctggcggc 120
gcaccagat gccagggcg aggtgcgctt gtctgtaccc ccgctggtgg aggtgatgcg 180
aggaaaagtct gtcattcttg actgcacccc tacgggaacc cacgaccatt atatgctgga 240
atggttcctt accgaccgct cgggagctcg ccccgcccta gcctcggtcg agatgcaggg 300
ctctgagctc caggtcacaa tgcacgacac ccggggccgc agtcccccat accagctnng 360
actyccangg ggcgcctggt ngctggnytg anggccark tggcgacgag c 411
```

<210> 26

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (634)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (652)

<223> n equals a,t,g, or c

<400> 26

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cagcccctct tcccttcctc cattgcacat gaacatatgt ccatccatat atattcatca 180
gaatgttaat ttattttgct ccctctgtta ggtccatttt ctaagggtag aagaggcaag 240
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tggtagggat gaggtctgat aagaacccag ggtggagagg gagactcctg ggcagccgtt 300
ttcctcatcc tttccctctc ccagtccatt tccaaatgtg gcctccatgt ggggtgctagg 360
gacatgggaa aaaccactgc tatgccattt cttctctctg ttccttccct ccccccgac 420
ggtgtggctg atgatgtctt ctggtgtcat ggtgaccacc ccctgttccc tgttctggta 480
tttccctgt cagtttcccc tctcggccag gttgtgtccc aaaatcccct cagcctcttc 540
tctgcacgtt gctgaaggtc caggcttgcc tcaagttcca tgcttgagca ataaagtga 600
aacaataaaa cctgggaaaa aaaaaaagg gggncgttct aaaggatccc cnagggg 657

<210> 27

<211> 1903

<212> DNA

<213> Homo sapiens

<400> 27

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agccaccatg aaggtggggg aggtgtgcca catcacctgc aaaccagaat atgcctacgg 180
ttcagcaggc agtccctcaa agattccccc caatgccacg cttgtatttg agtgaggatt 240
gtttgagttt aagggagaag atctgacgga agaggaagat ggcggaatca ttcgcagaat 300
acagactcgc ggtgaaggct atgctaagcc caatgagggt gctatcgtgg aggttgact 360
ggaagggtac tacaaggaca agctctttga ccagcgggag ctccgctttg agattggcga 420
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agagcggggc actgtgtact tcaaggagg taaatacaag caagctttac tacagtataa 720
gaagatcgtg tcttggctgg aatatgagtc tagtttttcc aatgaggaag cacagaaagc 780
acaggccctt cgactggcct ctcacctcaa cctggccatg tgtcatctga aactacaggc 840
cttctctgct gccattgaaa gctgtaacaa ggccctagaa ctggacagca acaacgagaa 900
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<210> 28

<211> 1333

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (1311)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1313)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1319)
<223> n equals a,t,g, or c

<400> 28
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agccgggtcga gggattccgc gtgacactgg tggacgaggg cgatctatac aactgggagg 120
tggccatctt. cgggcccccc aacacctact acgagggcgg ctacttcaag gcgcgcctca 180
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acccccagag cggggagctg ccctcagaga ggtggaaccc cacgcagaac gtcaggacca 360
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acgcctccgt gatgtacagg aagtggaaaag agagcaaggg gaaggatcgg gagtacacag 480
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ggagccacgt ccagcacaga gtggacggat tcaccgtggc cgactctttt ccctgctttg 1200
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa nanaaaaana 1320
aaaaaaaaaa ttt 1333

<210> 29
<211> 1327
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (573)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1307)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1325)
<223> n equals a,t,g, or c

<400> 29
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ccctggagga ggaagaagag ggaggcagag aggaagagga ggcgcccatg tatgaggagg 480
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acacaagctt cttgcctgat cgagaccgtg agnaggagga gaatcggctt cgggaagagc 600
tgcggcagga gtgggaagcc aagcaggaga agatcaagag tgaggagatc gagatcacct 660
tcagctactg ggatggctct ggcaccggc ggacagtcaa gatgagaaag ggcaacacca 720
tgcagcagtt cctgcagaag gcgctcgaga tccttcggaa agacttcagt gagctgaggt 780
ccgcagggkt ggagcagctc atgtacatca aggaggactt gatcatccct caccatcaca 840
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cgtgtcctgc ccctgccaca tcagtgactg ctttattctt ttccaataaa gaagtgcacg 1260
tgtcagagct ggagcgctg cattgtgaga aaaaaaaaaa gaggggnaag aaaaaaaaaa 1320
aggngg 1327

<210> 30
<211> 709
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (696)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (701)
<223> n equals a,t,g, or c

<400> 30

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aatcctagaa aactcacaaa atgtgtgatg ctttttagg tacctggaaa cttgtctcca 120
gtgaaaactt tgatgattat atgaaagaag taggagtggg ctttgccacc aggaaagtgg 180
ctggcatggc caaacctaac atgatcatca gtgtgaatgg ggatgtgatc accattaaat 240
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cactgcagat gacaggaaa tcaagagcac cataacctta gatgggggtg tcctggtaca 360
tgtgcagaaa tgggatggaa aatcaaccac cataaagaga aaacgagagg atgataaact 420
ggtggtggaa tgcgtcatga aaggcgtcac ttccacgaga gtttatgaga gacataagc 480
caaggagcgt tgacctggac tgaagtctgc attgaactct acaacattct gtgggatata 540
ttgttcaaaa agatattggt gttttccatg atttagcaag caactaattt tctccaagc 600
tgattttatt caatatggtt acgttggtta aataaacttt ttttagattt aaaaaaaaaa 660
aaaaaaaaac ycgggggggg gcccgttacc caattngccc nttaggggg 709

<210> 31

<211> 1108

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (389)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (397)

<223> n equals a,t,g, or c

<400> 31

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ccaaacaact ttaattgat ccagaagatg atgtaagaga taatatTTTA aaatatgatg 120
aagaaggtgg aggagaagaa gaccaggact atgacttgag ccagctgcag cagcctgaca 180
ctgtggagcc tgatgccatc aagcctgtgg gaatcygacg aatggatgaa agaccatcc 240
acgccgagcc ccagtatccg gtccgatctg cagccccaca ccctggagac attggggact 300
tcattaatga gggccttaaa gcggctgaca atgacccac agctccacca tatgactccc 360
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cctcaagtag tgggtgtgag caggactatg attacctgaa cgactggggg ccacggttca 480
agaaacttgc tgacatgtat ggtggaggtg atgactgaac ttcaggggtga acttggtttt 540
tggaacaagta caaacaattt caactgatat tcccaaaaag cattcagaag ctaggcttta 600
acttttagt ctactagcac agtgcttgc ggaggctttg gcataggctg caaaccaatt 660
tgggctcaga gggaaatatca gtgatccata ctgtttggaa aaacactgag ctgagttaca 720
cttgaatttt acagtacaga agcactggga ttttatgtgc cttttgtac ctttttcaga 780
ttggaattag ttttctgttt aaggctttaa tggtagtgc ttctgaaacg ataagtaaaa 840
gacaaaatat tttgtggtgg gagcagtaag ttaaaccatg atatgcttca acacgctttt 900
gttacattgc atttgcTTTT attaaaatac aaaattaaac aaamaaaaaa actcatggag 960
cgattttatt atcttggggg atgagaccat gagattggaa aatgtacatt acttctagtt 1020
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<210> 32

<211> 526

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (502)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (524)
<223> n equals a,t,g, or c

<400> 32
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tacacattta acacacagta gcaaattttg aacgatgtga ttgatataac ctaacaaatc 120
tgagccagtt attattagag ttgcagaata gaaacttgaa gtgctaaatg gaataatcca 180
aaggaaattt tttaaagca ggttctagct gaaaaattca actataagaa aattgtattt 240
atataacatt tactattttt gaagactagt gagatttctg taataatttt aattctttaa 300
aaagtgaag cttgttgtaa agatattttc ttttgttat tagaaggaaa tacaagaga 360
aaaatttctt tctttcatgg ggcatttgat aatttcagtc ttgacgatt tgtaagccta 420
gaataacta agctgaataa cagctcttg gcctcagaat tttccagtag ccagtawttc 480
yggattaact aagttgaaa cncytattag gaacctccag tggnga 526

<210> 33
<211> 555
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (494)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (521)
<223> n equals a,t,g, or c

<400> 33
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gctgtgtgcg cagggccccg caccggactg ggacctggc gtccctccag gccttgctc 120
ctgcgggags acagtttggc ttcacttctc tgacccagc ctgcggccta aagtgaaga 180
gaccggacca gtttcagctt tcggactctg gttcttgat cgtgtcctct cccctcgc 240
gccctcttcc ccaatctga gccattkag gcctctgcct gckgccccct ctctcctcg 300
gatcgggtcc ccagagccac catctcctga gcctcccacc ccgctgcctg ggccctgtg 360
ttgctgggcc tcccactca aggaggggaa ggtgtacag ccgaaccg tggagcaatg 420
ccctgtctgg cctccaaaac caaaataaaa ctgggtcact ttacaaaaaa aaaaaaaa 480
aaggggccccg gaanaccgga ccggtacctg caggcgtacc ngttcccta tagtgagttg 540
tattagcgtt gcata 555

<210> 34
<211> 347
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (288)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (328)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (335)
<223> n equals a,t,g, or c

<400> 34
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tgagggccct gtgggtgctg ggcctctcct gertcctgct gaccttcggg tcgggtccgar 180
ctgaygatga agtcgatgtg gatggtacag tggaagagga tctgggtaaa agtagagaag 240
gttcaaggac agatgatgaa gtagtacaga gagaggaaga agctattnca gttggatgga 300
ttaaattgcat cccaaataag agaacttnag agagnaagtc cagaaaa 347

<210> 35
<211> 750
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (701)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (731)
<223> n equals a,t,g, or c

<400> 35
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ttcttgctcc ttccagccat ggctctcaga gtccttctgt taacagcctt gacettatgt 120
catgggttca acttgacac tgaaaacgca atgaccttcc aagagaacgc aaggggcttc 180
gggcagagcg tgggtccagct tcagggatcc aggggtggtg ttggagcccc ccaggagata 240
gtggctgcca accaaagggg cagcctctac cagtgcgact acagcacagg ctcatgagag 300
cccatccacc tgcaggtccc cgtggaggcc gtgaacatgt ccctgggcct gtccctggca 360
gccaccacca gccccctca gctgctggcc tgtggtccca ccgtgcacca gacttgagct 420

gagaacacgt atgtgaaagg gctctgcttc ctgtttggat ccaacctacg gcagcagccc 480
cagaagttcc cagaggccct ccgaggggtgt cctcaagarg atagtacat tgccttcttg 540
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actgtgatgg agcaattaaa aaagtccaaa acctgttct ctttgatgca gtactctgaa 660
gaattccgga ttacttttac ttcaaagagt tccagaacaa ncctaacca agatcactgg 720
tgaagccaat nacgcagctg cttggggcgg 750

<210> 36

<211> 1291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (298)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (695)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (795)

<223> n equals a,t,g, or c

<400> 36

aagaaaaatg tactacgcct gtcctgtang aagctgaaga tttttgcaat gcccatgcag 60
gatatcaaga tgatcctgaa aatgggtgcag ctggactcta ttgaagattt gggaagtgc 120
ttgtacctgg aagctaccca ccttggcgaa attttctcct tacctgggcc agatgattaa 180
tctgcgtaga ctctctctct cccacatcca tgcattctcc tacatttccc cggagaagga 240
agagcagtat atcgccagct tcacctctca gttcctcagt ctgcagtgcc tgcagctnct 300
ctatgtggac tctttatttt tccttagagg ccgcctggat cagttgctca ggcacgtgat 360
gaacccttg gaaacctct caataactaa ctgccggett tcggaagggg atgtgatgca 420
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gaccgatgta agtcccagc ccctccaagc tctgctggag agagcctctg ccaccctcca 540
ggacctggtc tttgatgagt gtgggatcac ggatgatcag ctccctgccc tctgccttc 600
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tctgttcccc ctggagagtt atgaggacat ccattggtamc ctccamctgg agaggttgct 780
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agawtctggc ttgggaagta catgtaggag ttaatccctg tgtagactgt tgtaaagaaa 1260
ctgttgaaaa taaagagaag caatgtgaag c 1291

<210> 37

<211> 1535

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1413)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1526)

<223> n equals a,t,g, or c

<400> 37

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agtacgctgg gctggaccac gagctggcct tctctcgtct gatcgtggag ctgcggcggc 120
tgcacccagg ccacgtgctg cccgacgagg agctgcagtg ggtgttcgtg aatgcgggtg 180
gctggatggg cgccatgtgc cttctgcacg cctcgtctgc cgagtatgtg ctgctcttcg 240
gcaccgcctt gggctcccg gcaccctcgg ggcgctactg ggctgagatc tcggatacca 300
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catggatggt ggagtacggc cggggcgcta tccatccac cctggccttc gcgctggccg 480
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acacacacaa cacatacaca cacacacaca canacacata tcacagtttt cacacagccc 1440
ctgctgcatt ctctgtccat ctgtctgttt ctattaataa agatttgttg atctgttcca 1500
aaaaaaaaa aaaaaaaaaa aaaaangggg gggct 1535

<210> 38

<211> 295

<212> DNA

<213> Homo sapiens

<400> 38

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acacccgata gcgaaagtta tcgggtgttt tcttgaacat cgacggcgaa ggtaacccca 180
ttaatcacca gtcaaaactt ttcaccagcg tcactcgcca gcattacgca tcggtacaat 240
aaatgtttcc tgtttctcat tgaccgatcc ttcacgggtg atcagcgctca ttggg      295
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<210> 39

<211> 1300

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (641)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1297)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1298)

<223> n equals a,t,g, or c

<400> 39

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tctggaagtt aatggttttg agtgattttt aaatccttgc tggcggagag gcccgctctt 120
ccccggtatc agcgcttcct cattctttga atccgcggct ccgcggtctt cggcgtcaga 180
ccagccggag gaagcctgtt tgcaatttaa gcgggctgtg aacgcccagg gccggcgggg 240
gcggggccga ggcgggccat tttraataaa gaggcgtgcc ttccaggcag gctctataag 300
traccgcgcg ggcgagcgtg cgcgckttgc aggtcactgt agcgggaactt cttttggttt 360
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cccctggacc ccctgatggc cccacacctc ccatccagac agccgagctc gctccggaac 720
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gcggcggcag agctggctct ctggtctcct tggagaaagg ttctgttgcc ctgatttatg 1140
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caatgcgatg tatattaac tttttataaa agttaacatt ttgcataata aacgattttt 1260
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1300

<210> 40
<211> 215
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (210)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (213)
<223> n equals a,t,g, or c

<400> 40
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agaaagataa aattgtgtat tgtaacatg taaataaaat tggagctaatt tgaaactag 120
cttctcaata acttcattctt tctagagact cattacctgt gggcttgctm aacctggact 180
atttggccaa atwggttgga taaaaaaggn atntt 215

<210> 41
<211> 474
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (85)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (216)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (374)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (449)
<223> n equals a,t,g, or c

<400> 41
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gcccgagct gggtttctcg caagnctacg tgacccctcg gaggcccttt gagaagtcgc 120

ggctcgacca agagctgaag ctgataggcg agtacgggct ccggaacaaa cgtgaggtgt 180
ggaggggtcaa gttcaccctg gccaaagatcc gcaagnccgc gcgggarctg ctgacgctgg 240
acgagaagga cccgcggcgc ctgtttgagg gcaatgcctt gcttcggcga ctggtgcgca 300
ttggagtgtt ggacgagggc aagatgaagc tggattatat cctgggtctg aagatgagga 360
ttcttgagga grntctgca gacccaggtt tttcaagctg gggttggcca atccatccac 420
catgccctgt gctgatccgc caggccacnc aggtccgaaa gcaagtgggtg aaca 474

<210> 42

<211> 425

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (375)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (403)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (418)

<223> n equals a,t,g, or c

<400> 42

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accatgagaa catcacttgg accaaatgga cttgataaaa tgatggtgga caaggacggc 180
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cacgggggtg gttgtcctgg ccggcgccct gctggaagga ggccgagcag ctgctggacc 360
gcggcattca mccgntcagg atcgccgacg gttacgagca ggntgcccgc attggccntc 420
gagca 425

<210> 43

<211> 1187

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (33)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (41)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1149)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1156)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1160)
<223> n equals a,t,g, or c

<400> 43
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aagaccatca ccctcgaggt tgagcccagt gacaccatcg agaattgtcaa ggcaaagatc 180
caagataagg aaggcatccc tcctgaccag cagaggctga tctttgctgg aaaacagctg 240
gaagatggkc gcaccctgtc tgactacaac atccagaaaag agtccaccyt gcacctggtr 300
ctccgtctca gagtggggat gcaaattcttc gtgaagacac tcactggcaa gaccatcacc 360
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ggcattcctc ctgaccagca gaggttgatc tttgccgaa agcagctgga agatgggccc 480
accctgtctg actacaacat ccagaaagag tctaccctgc acctggtgct ccgtctcaga 540
ggtgggatgc agatcttctg gaagaccctg actggtgaag ccatcacact cgargtggag 600
ccgagtgaac ccattgagaa tgtcaaggca aagatccaag acaagggaagg catccctcct 660
gaccagcaga ggttgatctt tgctgggaaa cagctggaag atggacgcac cctgtctgac 720
tacaacatcc agaaagagtc caccctgcac ctggtgctcc gtcttagagg tgggatgcag 780
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accctgactg gtaagaccat cacyctcgaa gtggagccga gtgacaccat ygagaatgtc 1080
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aaarcttgna aatggncgan cccttttgat taaaatcccc aaagtcc 1187

<210> 44
<211> 515
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (217)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (465)

<223> n equals a,t,g, or c

<400> 44

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accggtctac ctgcgtagca tgctggggccg cggcaagact ggcggaagg cccgcgcca 120
ggccaagtgc cgtcgtctgc gcgccggcct ccagttccca gtgggcccgtg tacaccggct 180
gctgcggaag ggccactacg ccgagcgcgt tggcgcnngc rcgccagtgt acctggcggc 240
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caagaagacg cgaatcatcc cccgccacct gcagctggcc atccgcaacg acgaggagct 360
caacaagctg ctggggcggcg tgacgatcgc ccagggaagg cgtctgccc aacatccagg 420
ccgtgtgtg tgcccaagaa gaccagcgc accgtggggc cgaangccct tcggggggca 480
agaaagggca accaaggctt cccaaggagt actaa 515
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<210> 45

<211> 1499

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1476)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1492)

<223> n equals a,t,g, or c

<400> 45

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tccacttcag ctccccggca tccgcgaggt caccattaac cagagcctgc tggccccgct 120
gcggctggac gccgacccct cctccacgag ggtgcgccag gaggagagcg agcagatcaa 180
gacctcaac aacaagtttg cctccttcat cgacaagggt cggtttcttg agcagcagaa 240
caagctgctg gagaccaagt ggacgctgct gcaggagcag aagtcggcca agagcagccg 300
cctcccagac atctttgagg ccagattgc tggccttcgg ggtcagcttg aggcactgca 360
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caagaataag tacgaagatg aaattaaccg ccgcacagct gctgagaatg agtttgtggt 480
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catccggacc gcatccgcca gtcgcaggag tgccgcgac tgagccgcct cccaccactc 1320
```

cactcctcca gccaccaccc acaatcacaa gaagattccc acccctgect cccatgcctg 1380
gtcccaagac agtgagacag tctggaaagt gatgtcagaa tagcttccaa taaagcagcs 1440
tcattctgag gcctgagtga aaaaaaaaaa aaaaanaaaa aaaaaaattt tngggggggg 1499

<210> 46
<211> 393
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (167)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (178)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (219)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (359)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (372)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (378)
<223> n equals a,t,g, or c

<400> 46
tcgaaccacg cgtccggcag cctttctgag ggagcgggtg tgtgttcgcc atcttaggaa 60
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cagctggtac acgatggcct cacgggcacc gaagcagccc cgtgggnacc cccgggncg 180
ccccgaacgt tcccgaatc tggcagcagc cgctgtgna agagtacagt tgcgaatatg 240
gtcccatgaa gttttatgca ctgtgtggct ttggtgggt cttaaagtgt ggtctgacac 300
aactgctgt cgttcctctg gatttagtga aatgccgaat gcargtgga cccagaant 360
acaagggcak wnttaatngg attctcatta aca 393

<210> 47
<211> 238
<212> DNA

<213> Homo sapiens

<400> 47

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cgcgcccgga ccggttcaac ttctcatctt tgttcttctt catatactat aggctgtttg 180
ctgtggttta gtcaaaaagc catgtagaat gcctgccttt tgaagaccac ttttaagg 238
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<210> 48

<211> 939

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (937)

<223> n equals a,t,g, or c

<400> 48

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gccgcccga tgaacccga atatgactac ctgtttaagc tgcttttgat tggcgactca 120
ggcgtgggca agtcatgcct gtcctgcgg tttgctgatg acacgtacac agagagctac 180
atcagcacca tcggggtgga cttcaagatc cgaaccatcg agctggatgg caaaactatc 240
aaacttcaga tctgggacac agcgggccag gaacggttcc ggaccatcac ttccagctac 300
taccgggggg ctcatggcat catcgtggtg tatgacgtca ctgaccagga atcctacgcc 360
aacgtgaagc agtggtgca ggagattgac cgctatgccg gcgagaacgt caataagctc 420
ctggtgggca acaagagcga cctcaccacc aagaagggtg tggacaacac cacagccaag 480
gagtttcag actctctggg catcccttc ttggagacga gcgccaagaa tgccaccaat 540
gtcagcagc cgttcatgac catggtgct gaaatcaaaa agcggatggg gcctggagca 600
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ggctttgggg tgcctgggc tccccatctc cttctggccc atctgcctgc tgccctgagc 840
cccgttctk tmagggtccc taaaggagga cactcagggc ctgtggcagg cagggcggag 900
gctgcttggt ctgttgctc taagtgaatt tccaaangc 939
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<210> 49

<211> 1771

<212> DNA

<213> Homo sapiens

<400> 49

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tttgacagac actccaacca gctgtggaac atcagcgccg tcccttcctg gtccaaagt 120
aaccagggtc tcatccgcat gtataaggcc gactgcctgg agaagttccc tgtgatccag 180
cacttcaagt tcgggagcct gctgcccac catcctgtca cgtcgggcta ggaggggcca 240
agccgaagag ccacccaggc cacagttcct gtgcctgcct tccccacccc agcagtggcc 300
cctccccatc ccctccctct gttcgtcccg tttgatgaga ggctgtttac tggggtggg 360
tggcgagatg ggcttgaggg ggctcagagc ataaggcttc agggcccaag ttgggagaag 420
tgacaaaagt gttagcagtt ttctgagttc ccgtgtgcta gactggccag aagagagggt 480
ctggggcctg gtcactcggc cactctctcc tgtttctggc ctcttctccc ttcactccc 540
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tccagtctgg ttttgagagc aggggctggt ctgcagcacc kcagggaagg gaggagagat 600
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cacccttcc tggtccccc atccccctat ggctcccagc cccttgacc ctctattgtg 1680
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<210> 50

<211> 397

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (201)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (207)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (352)

<223> n equals a,t,g, or c

<400> 50

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aatcgctcgc acgcacgggc cctcgctcgc tcgcccgtcc gtgcccgcgc cggccagccc 120
accgccaccc ttgacagcca tgtccaccag gtcygtgtcc tcgtcytcct accgcagatg 180
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ccgcacctac agcctgggca gcgcctgcgc cccagcacca gccgcagcct ctamamctcg 300
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<210> 51
<211> 1635
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1422)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1617)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1620)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1629)
<223> n equals a,t,g, or c

<400> 51
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ccatcaaggg ctctccggc ctggggggcg gctcgtccc caccctctgc cggtgtctg 180
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tgcctgatga caataaagct tgttgactca gctaaaaaaa aaaaaaaaaa aaaaaaaaaa 1560
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaanttn 1620
gggggggggnc ccccc 1635

<210> 52
<211> 1780
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1780)
<223> n equals a,t,g, or c

<400> 52
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gggggtgatcc tgctggctgt tggagtctgg ggcaaaactta ctctgggcac ctatatctcc 180
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<210> 53
<211> 490
<212> DNA
<213> Homo sapiens

<400> 53

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catttctgga gcagggcctg agaccctgcc acatctccta tgctctgcat ccacgcctct 420
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aaaaaaaaaa 490

<210> 54

<211> 1944

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (466)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (634)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1308)

<223> n equals a,t,g, or c

<400> 54

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gcaacgtgaa ggtgctcggc aaggccgtcc actccctgtc ccgcacggg gacgagctct 180
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tggcccccag cccccaaga gccccggtcc cactccgag gaggaagatg aggctgagcc 1140

cagtacagtg cctgggactc cccaccccaa gaagttccgc tcaactgttct tcggctccat 1200
cctggccctt gtacgctccc cccagggccc cagcctgtgc tggcggaga cagtgagggt 1260
gaaggctgaa ccaagaacct gaagcctgta cccagaggcc ttggactnag acgaagcccc 1320
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tgagctgttt cactgcctct cgcaggcccc agctggctgt cactgtaaa ctgtcccaca 1440
gcggtcgggc ctgggcccgt atctccccac aamccccarc caatcaggac ttccagact 1500
tggccctgaa ctactgacgt tcctacctct tatttctcat tgagcctcag gctatactcc 1560
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gaagtccttg gcatgcatct gggacccccg tggagctgac aagttttctt tgctttcctg 1740
atactctttg gcgctgactt ggaattctaa gagccttgga cccgagtgtg tggctagggt 1800
tgccctggct ggggccccgt gccgagactc ccaagcggst ctgtgcagaa gagctgccag 1860
gcagtgtctt agatgtraga cggaggccat ggcgagaatc cagctttgac ctttattcaa 1920
gagaccagat gggtttgccc cagg 1944

<210> 55

<211> 994

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (896)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (971)

<223> n equals a,t,g, or c

<400> 55

cccccgtagc cagtaccggg tccgcgcctg tccccgaaac ttcgcacccc gtccaactct 60
cgcgagagcg ktatctgcyt gtcgggacgt gcggaggctc tcaactttccg tcatggcgct 120
gaaggtagcg accgtcgccg gcagcgccgc gaaggcgtgc tcgggccagc ccttctctgc 180
cgctccctggg aggttctagg cgcacacgag gtccctcga ggaacatctt ttcagaacaa 240
acaattcctc cgtccgctaa gtatggcggg cggcacacg tgaccatgat cccaggggat 300
ggcatcgggc cagagctcat gctgcatgac aagtcctctt tcaggcacgc atgtgtacca 360
gtggactttg aagaggtgca cgtgagttcc aatgctgatg aagaggacat tcgcaatgcc 420
atcatggcca tccgcgggaa ccgcgtggcc ctgaagggca acatcgaaac caaccataac 480
ctgccaccgt cgcacaaatc tcgaaacaac atccttcgca ccagcctgga cctctatgcc 540
aacgtcatcc actgtaagag ccttcaggc gtggtgaccc ggcacaagga catagacatc 600
ctcattgtcc gggagaacac agagggcgag tacagcagcc tggagcatga gagtgtggcg 660
ggagtgggtg agagcctgaa gatcatcacc aaggccaagt cctgcgcat tgccgagtat 720
gccttcaagc tggcgagga gagcgggcgc aagaaagtga cggccgtgca caaggccaac 780
atcatgaaac tgggcgatgg gcttttctc cagtgtgca gggaggtggc agcccggtac 840
cctcagwtca ccttcgagaa catgattgtg gataacacca ccatgcagct ggtgtncgg 900
ccccagcagt ttgatgtcat ggtgatgccc aatctctatg gcaacatcgt caaacaatgt 960
ctgcgcgagg ntggtcgggg gcccaagctt gttg 994

<210> 56

<211> 328

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (123)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (156)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<400> 56

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gggtcgaccc acgcgtccgc ccacgcgtcc ggatgacttc attgccaaag ttgttcaaag 60
gtagccttgg ccccttttca tctgagtccc atttagagat gtataaagaa tgttggtgag 120
tanggcgcgg tggctcacgc ctgtaatccc cacacnttgg gaaggccgan gcaggcggat 180
cacgagggtca gaagattgag accattctgg ctaacatggt gaaccccat ctctactaaa 240
aatacaaaaa ttagtcaggc gcgatggcgg gcacatgtag taccagctac tcgggaggct 300
gatgcagaag aataacttgg aacctggg                                     328
```

<210> 57

<211> 1489

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (710)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1109)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1117)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1206)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1211)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1218)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1264)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1311)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1446)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1467)
<223> n equals a,t,g, or c

<400> 57
cggcagcagg ggtggtgtgg gtgtgttttag aaaaaagatg cattcctgaa gatctctggt 60
gctgaagggc ctcgagtcc ttccagagac tgtatttgac acacttttagg tacacacaaa 120
cgaatggtat cacatgcaat attttaatgg agcaatggga gaggtctctt gaaatgggggt 180
ttgcatcttt ttgtaacatt ttgatttctc tgggtgcctta ttcctacttg atgctggcac 240
tcacataccc acaagaagct gacacagaag tcagccttag gcgtggggac atatgggtga 300
tgtttgagca tgcaggggcc atggggagtt tgggtgtcagt tgggtggagaa gggactagat 360
ggcatctctt agccgaggcc aacaggaact gcacaagtcc attatagtca aagttagcaa 420
ttttgatacg taaacacaat acttcattct tcctcatctg agctttcctt ccttcttcct 480
tttctatctc taccttctca taaaggtgct gctgctgctg ctaagggtgcc cggagtccag 540
aatgtccatt aatcactcag gcacgagcct ggcaactgcca cgtcagcccc cagcatgacc 600
aaaccaggt ttctcttgct tggggctgag aactgtcaga tttttctcat caaaaatggt 660
ttccaaggaa tcagtggatt acagttttct tgcattgaaa atgcacttn aaaaaataaa 720
ttaaagctcc agactgttta aaatatacag agggagcagg gaaaagttaa gcatgtgcta 780
gtgtctgaac ccagttcagt ttatctccag ttgaaacgat atacactata ttatgtataa 840
atgtatacac acttcctata tgatccaca tatatatagt gtatatatta tacatgtata 900
ggtgtgtata tgtgcatata tacacacatg cacataacaa aatcagatgc tcattacaaa 960
tccagatgct cattacaaaa ccagatgcta cacaacacgc agcagaggaa acaaggttgg 1020
actcttgcaa cagatcacia aaaataaaaa cagctacttg cagtgacttt ggtcatttct 1080
gtatgttcat aaagaatgga ttgtaacna ggaaaanaag gaccagtgtt agtgaaaagg 1140
gaagatgggg cgaaccatct tgatccgatg cgaatccgta atggtctata tacatttcat 1200


```

cagtantcat ntagtcangt gattgattca gttctgctat gaaacattgt aacacgtacc 1260
cacnactgac aactactcgt gagcgttcat taggagtgac ctaactttgc ntgcctgctc 1320
atgggacgag ctcccttaggt ggagataccg gggaaatagag aaagatgcac gtctctgcgt 1380
tgtcgcgtgc tttgaggggc ggtctttacc ttccgtgttg gagtcctccc tgagtcgggc 1440
gctggntgcg ggacacggcc cttctcngtg tcccaggcgc tgcctcatt 1489

```

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<210> 58
<211> 1283
<212> DNA
<213> Homo sapiens

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<220>
<221> misc feature
<222> (38)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (550)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (1242)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (1250)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (1260)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (1263)
<223> n equals a,t,g, or c

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<400> 58
aggtaatttg aattgagaga gagtaagtga cttgctgnaa aaaggggttaa tcaacagcag 60
agctgggatt tgaaccata actctgtcaa agcctccact cctaactcct gttcatgctc 120
ctgtggagaa aatgcttgta gtaacatatt ttaaattgtac taacaagacc agtcatgggm 180
aaatgtttct gagacaaatc tctagtttat gatttaaaac agtacgtttt cttacgtgac 240
gaaaacaaaa agtgtgttaa tttgttccca gtggttgaag ttatttgcca acaattttac 300
tgtttctctt catctgttta taggatttct ctgcctcttc caaacttttc ctccctgaac 360
ctgaggggta agcattttat ttccctttag gaaaaacgtc agctgcttgt aaccactgtg 420
tttatgtcaa agcatttcatt ttttttagga tatctgaaaa aatgccatat aagaaaaaam 480
tctataaaac atctatwatt ttcgaaccca agtacactct tgcattctaw gctttaagtt 540

```

```

aaatgcaaan tcctttttcc ttcttctctgc tgcaagtact atctcatcct gatgctcaag 600
agtgtcaggg cctgggtttc caaacagaga ctaccctaaa attatttggc gagtagtact 660
ttacacaatt gcctctcccc cacaatcat aattgtttca gtaaaatggg tacttggttt 720
ttccaagaaa aaactcggtt ttactcattt ttggcctggt tgtttattta gaaactaatc 780
tggattcact cctctggtt gataccact caaaaaggac acttctgatt aagacggttg 840
aaactagaga tggacagggt atcaacgaaa cttctcagca tcacgatgac cttgaataaa 900
aattgcacac actcagtga gcaatatatt accagcaaga ataaaaaaga aatccatatt 960
ttaaagaaac agctttcaag tgcttttctg cagtttttca ggagcgcaag atagatttgg 1020
aataggaata agctctagtt cttaacaacc gacactccta caagatttag aaaaaagttt 1080
acaacataat ctagtttaca gaaaaatctt gtgctagaat actttttaaa aggtattttg 1140
aataccatta aaactgcttt tttttttcca gcaagtatcc aaccaacttg gttctgcttc 1200
aataaatctt tggaaaaact maaaaaaaaa aaaaaaaaaam mngggggggg gcccggggtn 1260
ccnccggggg gcccaagttt tac

```

1283

<210> 59

<211> 740

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (696)

<223> n equals a,t,g, or c

<400> 59

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agaaggagcg cggggaggac gtacctgtg agatgcgagc cggccaacag cttgcaagca 60
tgctccgctg gaccgagcc tggaggctcc cgcgtgaggg actcggcccc cacggcccta 120
gcttcgcgag ggtgcctgtc gcacccagca gcagcagcgg cggccgaggg ggccgcgagc 180
cgaggccgct tccgctttcc tacaggcttc tggacgggga ggcagccctc ccggccgctg 240
tctttttgca cgggctcttc ggcagcaaaa ctaacttcaa ctccatcgcc aagatcttgg 300
cccagcagac aggcgtagg tgctgacggt ggatgctcgt aaccacggtg acagcccca 360
cagcccagac atgagctacg agatcatgag ccaggacctg caggaccttc tgccccagct 420
gggcctggtg ccctgcgtcg tcgttgcca cagcatggga ggaaagacag ccatgctgct 480
ggcactacag aggcagagc tggtggaacg tctcattgct gtagatatca gccagtgga 540
aagcacagggt gtctccact ttgcaacctt tgtggcagcc atgagggcca tcaacatcgc 600
agataggctt gcccgctcc cgtgccgaa aactggcgga tgaacagctc agttctgtca 660
tccaggacat ggccgtgcgg cacacttgct tcaatnaacc tggtagaggt agacgggcgt 720
tttcgtgttg gaggtggaa

```

740

<210> 60

<211> 1291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (147)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1211)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1283)

<223> n equals a,t,g, or c

<400> 60

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acttttnccc ctcccccttt cttttcccggt ctcacgcgcc aggccgcttg cacatgcgca 60
ttaggtacaa agcctcgctc tttgtcccca tctgtcgttc acacgaactc aagcctttgg 120
cattcggcag ccaatagaat ctaaganatg gcggaaaaat gattccgcct cgggagctaa 180
acttgattgg cagtttagct aaccaatcga gaacgccatt tgtamccctt ggcaggcamc 240
gagctccgtc gtctcgtttc cggcggtcgc gcgctctttt ctcgggacgg gagaggccgt 300
gtagcgtcgc cgttactccg aggagatacc agtcggtaga ggagaagtcg aggttagagg 360
gaactgggag gcactttgct gtctgcaatc gaagttgagg gtgcaaaaat gcagagtaat 420
aaaactttta acttgagaaa gcaaaacccat actccaagaa agcatcatca acatcaccac 480
cagcagcagc accaccagca gcaacagcag cagccgccac caccgccaat acctgcaaat 540
gggcaacagg ccagcagcea aaatgaaggc ttgactattg acctgaagaa ttttagaaaa 600
ccaggagaga agaccttcac ccaacgaagc cgtctttttg tgggaaatct tcctcccgac 660
atcactgagg aagaaatgag gaaactatct gagaaatatg gaaaggcagg cgaagtcttc 720
attcataagg ataaaggatt tggctttatc cgcttggaag cccgaaccct agcggagatt 780
gccaaagtgg agctggacaa tatgccactc cgtggaaagc agctgcgtgt gcgctttgcc 840
tgccatagtg catcccttac agttcgaaac ctctctcagt atgtgtccaa cgaactgctg 900
gaagaagcct tttctgtgtt tggccaggta gagagggtg tagtcattgt ggatgatcga 960
ggaaggccct caggaaaagg cattgttgag ttctcaggga agccagctgc tcggaaaagct 1020
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gagcccatgg accagttaga tgatgaagag ggacttccag agaagctggt tataaaaaac 1140
cagcaatttc acaagggaag agagcagcca cccagatttg cacagcctgg ctcctttkga 1200
gtatgaatat ngccatgcgc tgggaaggca ctcattgaga tggagaaagc agcctggggg 1260
gacaagaagt gaagactcct gnttccaaaa a 1291
```

<210> 61

<211> 971

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (856)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (886)

<223> n equals a,t,g, or c

<400> 61

ctgcagtacc ggtccggaat tcccgggtcg acccacgcgt ccgggtctgt ggtcctctct 60
cggtctctcg cggtctcgcg cgcccgacgg ttcctgggac acctgcttgc ttggcccgtc 120
cggcggctca gggcttctct gctgcgctcc cggttcgctg gacgggaaga agggctgggc 180
cgtcccgtcc cgtcccatc ggaaccccaa gtcgcgccgc tgaccgctcg cagggcgaga 240
tgagcgcgga cgcagcggcc ggggcgccc tgccccgct ctgctgcctg gagaagggtc 300
cgaacggcta cggtctccac ctgcacgggg agaaggga gttgggccag tacatccggc 360
tggtggagcc cggtctcgcc gccgagaagg cggggctgct ggcgggggac cggtggtgg 420
aggtgaacgg cgaaacgtg gagaaggaga cccaccagca ggtggtgagc cgcattccgc 480
ccgcactcaa cgccgtgcgc ctgctggtgg tcgaccccg gacggacgag cagctgcaga 540
agctcgccgt ccaggtccga gaggagctgc tgcgcgccca ggaagcgcg ggcagggccg 600
agcccgccgc cgccgccrag gtgcaggggg ctggcaacga aaatrarcct cgcraggccg 660
acaagagcca cccggagcag cgcgagcttc ggcctcgct ctgtaccatg aagaagggcc 720
ccagtggcta tggcttcaac ctgcacagcg acaagtccaa gccaggccag ttcattccgt 780
cagtggaccc agactcccc gctgaggctt cagggctccg ggcccaggat cgcattgtgg 840
aggtgatgct tctcgncttct ctctctatct gaactgcccc caaccnctgc agattagcag 900
caccttgggg cagccatcat accatcatgg ggtttgatta gcccacgggc attagccaac 960
ctgggaggtt g 971

<210> 62

<211> 618

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (563)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (598)

<223> n equals a,t,g, or c

<400> 62

gggtcgaccc acgcgtccgg cagaaatgaa ggaccacctg ccaagacgaa gagctgggtg 60
ggaccacgc tgcattttca tcgaaagagt gaacatctag tgggactgaa agttctttgt 120
tgtttcagat tgtagagtgt gattgatgga attggtctgt ggaattgca ttgtttttat 180
ttctttatgt aatcagttta agtaataggg ggtatatata atcgtaagta ttttaggggtg 240
ggaggggcta ttaagtaatt aagtgggtgg ggttagttta aaagtttagca tgatatgtat 300
tagataactc tataagtgga catgtgtact tacttgtgat cttttaccct atgattgcta 360
cccttaacga tttcaataa actcagaggg aactgcaggg agatcaaacc atttagggca 420
aattggacat gaataaaact ctagtgggaa aaagttaaaa ggtgattgaa taaataattt 480
aactttgccc tgggtattaa gtccagggct cccagattgt ggagcagagc cttggagagt 540
acaggatgaa ggagatagat gcncctttga cttgccggga atgaaattgg attaatgnaa 600

ggatggtaaa taattcca

618

<210> 63

<211> 1138

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (15)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (22)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1123)

<223> n equals a,t,g, or c

<400> 63

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cgctccgatg acttcacccc tctggagatc ctctggacct tctccatcta cctggagtca 120
gtggccatct tgccgcagct gttcatggtg agcaagaccg gcgaggcgga gaccatcacc 180
agccactact tgtttgcgct aggcgtttac cgcacgctct atctcttcaa ctggatctgg 240
cgctaccatt tcgagggtt cttcgacctc atcgccattg tggcaggcct ggtccagaca 300
gtcctctact gcgatttctt ctacctctat atcaccaaag tcctaaaggg gaagaagttg 360
agtttgccgg catagccccg gtcctctcca tctctctcct cggcagcagc gggaggcaga 420
ggaaggcggc agaagatgaa gagctttccc atccaggggt gactttttta agaaccacc 480
tcttggtgct cccatccgc ctctgcgg gtttcagggg gacagtggag gatccaggtc 540
ttggggagct caggacttgg gctgtttgta gtttttgcc ttttagacaa gaaaaaaaaa 600
tctttccact ctttagtttt tgattctgat gactcgtttt tcttctact tgtggcccca 660
atttttataa agtgtttttg agtgcctat gggccggggc agggccaag atcttttccc 720
ttccccaggc ccctcggtc cctccagat cccaccccca gccccactgg ttgccaaca 780

ctaaatctgc cgacacccat ctgccccacc tcctgccatg gccatgaacc gcgacccccca 840
ctaaatttct agattgggga tagggagaaa gggaggccca ggaaggtctc ccctgatttt 900
ttttcatagt aatttttttc cccagagttt gaattttttg gtcttctcct ggtttttttg 960
caaattaggg gggcccgggg ctcaagtgcg ggaagggggc tggcccagg atcccatggc 1020
tctcacacca tgtttttgta cagaactgat ggttgaatct ttgttctctt gaaataaaca 1080
gaagaaaatg aaaccttaaa aaaaaaaaaa aaaaaaaaaa acncgggggg gggcccgg 1138

<210> 64

<211> 418

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (365)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (371)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (380)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (391)

<223> n equals a,t,g, or c

<400> 64

tgctcatcca gaggagctca ccacagtcac tgcgacagac tgccacactc accctggcct 60
ggcctcagag aagttgagct actggcctca gttcacacag agcagatgga ggaagagctg 120
gcactaggac ccagggggca ggggggagcc tccctggctg gaagggatgg caggagcgct 180
gggtgcaggta gctatggagc tctggccaac tctgcctggg gaggtcccag gaaggtggcg 240
tcagcatctg cagccgcgtc gacgttgctg gagcctccgc ggaggaccca ggagagccgg 300
actaggacca gggccctggg cctccccaca ctcccatgg agaagctggc ggcctctaac 360
agagncccaa ngggcttggc cggtcctggg ncgtgaaaat gttcaagtgc ccgattga 418

<210> 65

<211> 2836

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2834)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2836)

<223> n equals a,t,g, or c

<400> 65

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aagaaaccgc ccattacaca cccagtaga ccagcagagg aaacttataa cctcgggagg 60
caggtccttc ccctcagtgc ggtcacatac ttccagaaga gcggaccagg gctgctgcca 120
gcacctgcca ctccagagcgc ctctgtcgtc gggacccttc agaactctct ttgctcacia 180
gttaccacaaa aaaaaagagc caacatgttg gtattgctgg ctggtatctt tgtgggtccac 240
atcgctactg ttattatgct atttgtagc accattgcca atgtctggtt gggttccaat 300
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<210> 66

<211> 2305

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1973)

<223> n equals a,t,g, or c

<400> 66

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<210> 67

<211> 1907

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1221)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1655)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1896)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1904)

<223> n equals a,t,g, or c

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<210> 68

<211> 815

<212> DNA

<213> Homo sapiens

<400> 68

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<210> 69

<211> 1150

<212> DNA

<213> Homo sapiens

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<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (25)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1150)

<223> n equals a,t,g, or c

<400> 69

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gaaaaaaaaa                                     1150
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<210> 70

<211> 344

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (287)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (333)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (339)

<223> n equals a,t,g, or c

<400> 70

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<210> 71

<211> 448

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (425)

<223> n equals a,t,g, or c

<400> 71

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<210> 72

<211> 2825

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1809)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2093)

<223> n equals a,t,g, or c

<400> 72

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<210> 73

<211> 510

<212> DNA

<213> Homo sapiens

<400> 73

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ggacaagcga acactagcac tcctgggtgt agcccactcc tctgatgtgc tagagaatgt 240
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agaactggac cctgaagtgg aagggacaaa gccyagtgcc acagaratga tctgggctgt 360
gctggcagcc tttyaataaa tcytaaagcc rgyrggtggg tttctycttt tccccctgtg 420
gctgggtgact gttagagagac mcccactga gttttgtgtg atgasatgtt ttccatcatt 480
ttttccttyc ttgaatcaga cttgtgaatt 510

```

```

<210> 74
<211> 458
<212> DNA
<213> Homo sapiens

```

```

<220>
<221> misc feature
<222> (382)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (388)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (424)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (448)
<223> n equals a,t,g, or c

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<400> 74
gggtcgaccc acgcgtccgc tccacttaaa attcaacttc tgcttggttc atctgattct 60
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gcctcctggg tcttgataac ttcagtgttt ctgggagctg cccgggtggc caccagtctc 180
tgtggaatcc aggggcctct tcccaatatg gatttgacca gcacttcaat tagtgagttt 240
ccatkgacat cttagcatta ctctttaata cagacgcctt attttccagg gtttatgaaa 300
gtttaagtga caaccatgga ttgcaggaac agactgttga gaagctgttt ttccagtgga 360
aaagttgggt ccaggagatg angggagnct tgaaatagat cctgggatgg aaacataaag 420
tggncagcca gattcccatc atgggctncc ccataaaa 458

```

```

<210> 75
<211> 377
<212> DNA
<213> Homo sapiens

```

```

<400> 75

```

gtcctggaaa cacatcaagc tcagctcctg tgtccagctc gcttctctgc tggactcctt 60
gatttttttt ttaatcattg tttgattttg agcagtaacc aggctttttt ttccagatgt 120
tagtccacac ctattcatcc atggaccggc acgatggtgt cccgagccac agctcgcggc 180
tctcccagct gggctcgggtg tcccaaggac cctactcgag cgccccgccc ctgtcccaca 240
ccccgtcgtc ggacttccag ccgccctact tcccamcccc ctaccagccg ctccccctamc 300
amcagagcca ggacccttac tcccacgtca amgamcccta tcctgaacc cactgcacca 360
gccccagcaa catccct 377

<210> 76

<211> 2070

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (39)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2068)

<223> n equals a,t,g, or c

<400> 76

tcatgaatgg gaatcctggn cccaagaact ccgcttgcn g cagagggac ctgcagctga 60
ggacctatag cgttgtgccc atgacctnca gtgtatccca gggcacccgc gtgtgtaata 120
taaagattgg ctgacaaaaa tgtcaggaaa acatgatgtt ggagcttaca tgctaata 180
taagggcgct aatcgactg aaacagtcac gtcttttaga aaacgagaaa gtaaagtgcc 240
tgctgatctc ttaaagcggg ccttcgtgag gatgagtaca agccctgagg ctttcctggc 300
gctccgctcc cacttcgcca gctctcacgc tctgatatgc atcagccact ggatcctcgg 360
gattggagac agacatctga acaactttat ggtggccatg gagactggcg gcgtgatcgg 420
gatcgacttt gggcatgcgt ttggatccgc tacacagttt ctgccagtcc ctgagttgat 480
gccttttcgg ctaactcggc agtttatcaa tctgatgtta ccaatgaaag aaacgggcct 540
tatgtacagc atcatgttac acgcactcgg gcctttccgc tcagaccctg gcctgctcac 600
caacaccatg gatgtgtttg tcaaggagcc ctcccttgat tggaaaaatt ttgaacagaa 660
aatgctgaaa aaaggagggt catggattca agaaataaat gttgctgaaa aaaattggta 720
ccccgacag aaaatatgtt acgctaagag aaagttagca ggtgccaatc cagcagtcac 780
tactttgat gagctactcc tgggtcatga gaaggccct gccttcagag actatgtggc 840
tgtggcacga ggaagcaaa atcacacat tcgtgcccga gaaccagaga gtgggctttc 900
agaagagact caagtgaagt gcctgatgga ccaggcaaca gaccccaaca tccttggcag 960
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tgaaacacta aagagaaatg tcttttgtgc tacagtttcg tagcatgagt ttaaatacaag 1140
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acttgatatt ggaggctctt ctgtgatttt gagaagtata ctcttgagtg ttttaataaag 2040
tttttttcca aaaaaaaaaa aaaaaaantt 2070

<210> 77

<211> 997

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (619)

<223> n equals a,t,g, or c

<400> 77

ctcgccctcc tgactcttcc tgcaggtggc tcaggaagga ttcagcctgg ccacttggct 60
aggactctgc cagcaccat ctgagactga cctcttccgg gcctttggac actatgacct 120
tgatgctgcc cttcaggcag gaaacagggc tgggtgccttt tttcacctgc atggccagct 180
tccttccctg gcagtgagga gggcagccaa caggttctaa tgtcagagcc atcctttacc 240
aggtgggcct gcttgcctt gtcttgctg ccacatcact ctacttttg gaaggccatg 300
gctgattaaa gaagttcttg tagtttccca agcaaagtgg aatctagaaa cagtgaataa 360
agttcagata actttgaatt gcattcaaga agtacacttc tttcccatg tccgtggctc 420
ttggagtctc cgtgatgcca ggctagagtc tgattatata ataattcaaa atggttaactc 480
ccaaggtaat gctttcttcc atttcacag gttcttttat ccccaactgca cccctctccc 540
ttctcccttg cctatctgga tggcttctca gaagctcggc cctagtcctc cctgccttgg 600
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aaggtgaggt gtttttcttt tttgtaataa tataaagctg tgtgtttctg attggatgat 960
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<210> 78

<211> 1333

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1254)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1297)

<223> n equals a,t,g, or c

<400> 78

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agcgcragct tcggcctcgg ctctgtacca tgaagaaggg cccagtggc tatggcttca 180
acctgcacag cgacaagtcc aagccaggcc agttcatccg gtcagtggaac ccagactccc 240
cggtgagggc ttcagggtcc cggggccagg atcgcatgtt ggaggtgaac ggggtctgca 300
tggaggggaa gcagcatggg gacgtggtgt ccgccatcag ggctggcggg gacgagacca 360
agctgctggt ggtggacagg gaaactgacg agttcttcaa gaaatgcaga gtgatcccat 420
ctcaggagca cctgaatggt cccctgcctg tgcccttcac caatggggag atacagaagg 480
agaacagtcg tgaagccctg gcagaggcag ccttggagag ccccaggcca gccctggtga 540
gatccgcctc cagtgcacac agcagaggagc tgaattccca agacagcccc ccaaaacagg 600
actccacagc gccctcgtct acctcctcct ccgaccccat cctagacttc aacatctccc 660
tggccatggc caaagagagg gccaccaga aacgcagcag caaacgggcc ccgcagatgg 720
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caccctccct tcctcccca tgtgataaat ggggtccagg ctgatcaaag aactytgact 1140
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cttgttttca ttgatttttg ttaagagtgc agtattgcag agtctagagg aatntatgtt 1260
tccttgatta acatgatttc ctggttggtta catccanggc aggcagtggc tcagctttaa 1320
atttggttcc cta
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1333

<210> 79

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (542)

<223> n equals a,t,g, or c

<400> 79

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caatggggct gaggtgtgt ccactgaggc taagatgact gcctttcctg attggccttg 60
gcttttccat acattgtgtg acccttgccc tatgacctt tggctgacct taccggaagc 120
catgacgaca gcagcctttt gccattagac gcagggtgat ggtgaggatt ccaagggtta 180
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gacaaaactg gttaatctga actaggtgac tgttaccttg cgtgttttgt ggccaaacca 240
ccaccaaaaa cctcacactg tgatgtaagt acttagtgta aaactagtaa acatttttgt 300
aaaatgtaga aatgcatgta atcagttaag ttttatattt tacaatgttc tgtaaaataa 360
aacttagcga ggtaaactga ataaaggagc agtcactctc taacagattg taqqaqaagt 420
ttagttggat ttagtctatt tgacttgccc ttaatttaat tttatggcaa atcacaaatg 480
tgtcgaaggt ttagcaatat aatagcaaag tcctactcca gtaaataaaa gttggtatgt 540
tngtacttaa ctttcaaaag 560

<210> 80

<211> 3203

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1116)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1443)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1942)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3188)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3201)

<223> n equals a,t,g, or c

<400> 80

cggtacgcgt gggtcgcggg cttcgggggt ctgcgctcgc ggctgcctgg actcagcagg 60
ccccggacc atgtcccgcg ccctgcggcc accgctcccg cctctctgct ttttcctttt 120
gttgctggcg gctgccgggtg ctcggggccgg gggatacgag acatgcccc aagtgcagcc 180
gaacatgctg aacgtgcacc tgctgectca cacacatgat gacgtgggct ggctcaaaac 240
cgtggaccag tacttttatg gaatcaagaa tgacatccag cacgccgggtg tgcagtacat 300
cctggactcg gtcattctctg ccttgctggc agatcccacc cgctcgcttca tttacgtgga 360
gattgccttc ttctcccgtt ggtggcacca gcagacaaat gccacacagg aagtcgtgcg 420
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ggacacattt ggcaatgatg ggcgaccccg tgtggccttg cacattgacc ccttcggcca 600
ctctcgggag caggcctcgc tgtttgcgca ratgggcttc gacggcttct tctttgggag 660
ccttgattat caagataagt gggtagcgat gcagaagctg gagatggagc aggtgtggcg 720

ggccagcacc agcctgaagc ccccgaccgc ggacctcttc actggtgtgc ttcccaatgg 780
ttacaacccg ccaaggaatc tgtgctggga tgtgctgtgt gtcgatcagc cgctgggtgga 840
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<210> 81

<211> 1710

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1424)

<223> n equals a,t,g, or c

<400> 81

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tgtgggaggg cgtgggtggg gccgctgagc gcttccgggc ccggactggc acggagctgg 120
tgctgctgac cgcggccccc ccgcaccacc ccgcccgggc ccctgtgcct atgctgcca 180
tggtcgagga gccctggcgg aggcagcgcg ccgttgccctc cagcacatcg cactggccca 240
cagggtgccc actgctgctc ggccctcctgc gccccacca gcaccacagc caccagtc 300
cacaccagc ccaccccggc ctaccctggc cagagaggac aacgaggagg acgaggatga 360
gcccacagag acagagacct ccggggagca gctgggcatt agtgataatg gagggctctt 420
tgtgatggat gaggacgcca ccctccagga ccttcccccc ttctgtgagt cagacccca 480
gagtacagat gatggcagcg tgagcgagga gaccccgccc ggccccccca cctgctcagt 540
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tggtaccagc tcccgcctcc cgcgcccccac ctccacaggt gccttaaagg gccctcgtca 1560
cccaagggtg ggcaggggc cctcactctc cggccctggg gtgggggaga gaggaggagg 1620
ttgggggata ggcagttggg aggggcgctc tgagattaaa gaggttttacc tctgagataa 1680
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1710
```

<210> 82

<211> 1379

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (280)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1365)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1378)

<223> n equals a,t,g, or c

<400> 82

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gacgctgggc ctgcagcgcg gagcagaaag cagaacccgc agagtcctcc ctgctgctgt 120
gtggacgaca cgtgggcaca ggcagaagtg ggccctgtga ccagctgcac tggtttcgtg 180
gaaggaagct ccaggactgg cgggatgggc tcagcctgta tcaaagtcac caaatacttt 240
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<210> 83

<211> 678

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (602)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (626)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (648)

<223> n equals a,t,g, or c

<400> 83

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ccaacatgtc ccgtgggtcc agcgcgggtt ttgaccgcca cattaccatt ttttaccaccg 180

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ttttaattgg tatagatgaa gagcaaggcc ctcaggtata taagtgtgat cctgcagggt 600
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ccttgaaaaa aaagtgga 678

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<210> 84

<211> 2803

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (50)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (517)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (572)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1926)

<223> n equals a,t,g, or c

<400> 84

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tgtcagcaga gtccgtcaga cgtgagaagg gtgggagcgg cggactgtga acgctggtag 360
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cttccgggtg catagctgtg ggatccggaa gtaaaaacac aagccccgcs cccrrgaact 480
cggaagccg gcgakaagtg tgaggccgcy gtagggncgc atcccgtcc ggagagaagt 540
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aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aag 2803

<210> 85

<211> 1278

<212> DNA

<213> Homo sapiens

<400> 85

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gttttactca gtgaacgcca ggtccttct ccccgaggca gactacttct ctggggtgca 300
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cctggaagag cagaggatgg aggggaagaa gcccagggtg atggcaggca ccttgaagct 600
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aaaaaaccca cgcgtccg 1278

<210> 86

<211> 2585

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2573)

<223> n equals a,t,g, or c

<400> 86

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<210> 87
 <211> 385
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (385)
 <223> n equals a,t,g, or c

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<400> 87
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actgactaca tcaaagtcta ctacaccttg agaaaacaaa tgaacgaaa tctattttcc 180
tcattcatta ccccaacaa aataggactc cctatcgtaa ttattatcac tatgtttcca 240
agcattatat tcccacacc taccgactr aatcaataat cgactscatc tccattccaa 300
caatgattag tgcactgaac atscaaaaca aatrttgatc catgccacaa caaaaaagga 360
caaaactggag cccggatatt gatan

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<210> 88
 <211> 2500
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (429)
 <223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (1088)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2480)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2482)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2491)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2497)
<223> n equals a,t,g, or c

<400> 88
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<210> 89

<211> 1409

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (841)

<223> n equals a,t,g, or c

<400> 89

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catcgatgag gctggccact gcatggagcc tgagaagtct ggtagctata gcagggtga 180
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1409

<210> 90

<211> 1336

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (49)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1284)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1317)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1333)

<223> n equals a,t,g, or c

<400> 90

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gtcacgtact cttgcaattg cccgcaacct gactcagcag ctccagacca cgtgccacac 420
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1336

<210> 91
<211> 787
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (677)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (725)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (742)
<223> n equals a,t,g, or c

<400> 91
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acaagtg 787

<210> 92
<211> 1657
<212> DNA
<213> Homo sapiens

<400> 92
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ggacaatgac tacaggacac aatgtggctg acctggtggt gataactcaag attctgccaa 480

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ctacagtga gattctcatt acaacagtgc caccatctc tcgaaaactg gatccagaac 660
tccatttgga tatcaaagta ttgcagagtg ccttaqcaqc catccgacat gcccgctgg 720
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aaatgttaag tgtctgaaa ttttttttc taagaaaaac tattaagta cttcctagta 1620
ggaaaaaaaa aaaaaaaaaa aaacycgggg gttttct 1657

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<210> 93

<211> 485

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (478)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (485)

<223> n equals a,t,g, or c

<400> 93

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tgagagtgtc ccaggggatt cagagtctcc agaaagatat ggctrggcca actctgttgc 120
ctacctrgcc tgacccagtc ggagcctgac atggtggagg gaaagggaga caagtggggc 180
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actcatcgag acaacatgcc cagttatcag ggagtcctgt gtcacaaggt ctgtctctgc 360
cattgtaagc aagtgccttg ggcagctgg cctctgcccc acagtctcat ctgtacaccg 420
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485

<210> 94

<211> 764

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (202)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (565)
<223> n equals a,t,g, or c

<400> 94
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grtggtgga gaaccaggac cccagagagg tggggccact gaggctggtg cagttgcgct 180
cactcatcag catggcccgg angtggggg gcatcgggca taccacagca ggcccctatg 240
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caatcatctc agtggcgaag cacaccactt gattctatct ttttttaaca cattaaatct 720
gtttttaaag ataaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaa 764

<210> 95
<211> 707
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (45)
<223> n equals a,t,g, or c

<400> 95
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ccacgcgtgc catcatggcg caggatcaag gtgaaaagga gaaccccatg cgggaacttc 120
gcatccgcaa actctgtctc aacatctgtg ttggggagag tggagacaga ctgacgcgag 180
cagccaaggt gttggagcag ctacagggc agaccctgt gttttccaaa gctagatata 240
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gtatcaaata tgacccaagc attggtatct acggcctgga cttctatgtg gtgctgggta 480
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ctggcaataa aattcccgtt tctatccaaa agagcaataa aaagttttca gtgaaaaaaa 660
aaaaaaaaaa aaaaaaaggg ggcccccttt tgggggtccc ctggggg 707

<210> 96

<211> 815
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (16)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (50)
<223> n equals a,t,g, or c

<400> 96
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caagcccgaa gatgcccccc attctctwag tgatggcggc gttagggttt gagagaagg 180
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atgtacgctg ctgcaggaca ttaataaagt tgctttttta ggctacagtg tctcgatgcc 480
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gattgattga ttactattaa ctacaaggta taatttacta tcaccttatt taaattttat 720
gaattaattt gaatgttttt tacactaact aacttttccc aataaagtcc actatgaaac 780
cacgacaaaa aaaaaaaaaa aaaaaaaaaa aaaaa 815

<210> 97
<211> 658
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (627)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (634)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (635)
<223> n equals a,t,g, or c

<400> 97
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tgcccaagat gctgtacccc gagtaccaca aggtgcacca gatgatgcgg gagcagtcca 180
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<210> 98
<211> 249
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (248)
<223> n equals a,t,g, or c

<400> 98
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agactscctt tagagataga gaaacagacc caagaaatgt gctcaattgc aatggggccac 120
atacctagat ctccagatgt catttccctt ctcttatttt aagttatgtt aagattacta 180
aaacaataaa agctcctaaa aaatcaaaaa aaaaaaaaaa aaaaaaaaaa aaccccgggg 240
ggggcccnng 249

<210> 99
<211> 752
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (612)
<223> n equals a,t,g, or c

<400> 99
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<210> 100

<211> 3059

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (14)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (28)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (109)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3019)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3047)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3058)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3059)

<223> n equals a,t,g, or c

<400> 100

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<211> 1682
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (52)
<223> n equals a,t,g, or c

<400> 101
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tccaccagac gtctcctaag acagagttag agtcaacaat ctttggcagt ccgaggctgg 120
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1682

<210> 102
<211> 938
<212> DNA
<213> Homo sapiens

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<222> (30)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (812)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (913)
<223> n equals a,t,g, or c

<400> 102
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<210> 103
<211> 2012
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1993)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2002)
<223> n equals a,t,g, or c

<400> 103
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2012

<210> 104

<211> 1094

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<400> 104

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<210> 105

<211> 2297

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (30)

<223> n equals a,t,g, or c

<400> 105

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<210> 106
<211> 442
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (419)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (423)
<223> n equals a,t,g, or c

<400> 106
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<210> 107
<211> 1019
<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (995)
<223> n equals a,t,g, or c

<400> 107
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<210> 108

<211> 711

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (642)

<223> n equals a,t,g, or c

<400> 108

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<210> 109

<211> 743

<212> DNA

<213> Homo sapiens

<400> 109

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atttcatatt atataattct gcttattctt tcaaaaattt atacatccat tgggcaagga 180
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tttcatttcg tacaaaagtc acc 743

<210> 110

<211> 795

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (645)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (737)

<223> n equals a,t,g, or c

<400> 110

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<210> 111

<211> 1332

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (6)
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<220>
<221> misc feature
<222> (1194)
<223> n equals a,t,g, or c

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<222> (1237)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1241)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1300)
<223> n equals a,t,g, or c

<400> 111
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acggggagcc cttctctccc tggaccctg ggcttgnntc ntgggggggc tcttccaaga 1260
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aaggcaaaag ag 1332

<210> 112
<211> 743
<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (53)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (272)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (275)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (278)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (590)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (618)

<223> n equals a,t,g, or c

<400> 112

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ggtaacggcc tccaccgacg ggatcggett cgcacgccc ggcgtttggc ccaggacagg 180
gccacgtggt cgtcagcagc cggaagcagc agaattgtga ccaggcgggt gcacgctgca 240
rggggagggg ctgagcgtga cgggcacctg tncantgntg ggggaaggcgg aggaccggga 300
gcggctgtgt gccacggctg tgaagcttca tggaggatc gatatactag tctccaatgc 360
tgctgtcaac cttttctttg gaagcataat ggatgtcact gaggaggtgt gggacaagct 420
ctggatggac aaggaaaaag aggaaagcat gaaagaaacc ctgcggataa gaaggttagg 480
cgagccagag gattgtgctg gcatcgtgtc ttctctgtgc tctgaagatg ccagctacat 540
cactggggaa acagtgggtg tgggtggagg aaccccgctc cgcctctgan ggaccgggag 600
acagcccaca ggccagantt gggctctagc tcctggtgst gttcctgcat tcamccaytg 660
gscttttccc acctytgytc amcttactgt tcacctcatc aaatcagttc tgccctgtga 720
aaagatccag ccttcctgc cgt 743
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<210> 113

<211> 1690

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (1659)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1664)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1676)
<223> n equals a,t,g, or c

<400> 113
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ttggctgcag tccagctgcc agatggcttc aacctgctct gcccaacccc accacctccc 120
ccagacacag gccccgagaa gctgccatca ctggagcacc gggactcccc ttggcaccga 180
ggccccgccc ctgccaggcc taaaatgctg gttatcagtg gaggtgatgg ctatgaggac 240
ttccgactca gcagtggggg cgccasagca gtgagactgt gggtcgagac gacagcacia 300
accacctyct cctgtggagg gtgtgacctt gtctgccgtg gcccaggact sgccccccca 360
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agccagggga cacatgtgcy kgertgggct ctgcttgtct tcgcggaaga ttctgatgg 480
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gaccccccaa agctgagggg ctgaatgtag ccttttcaac agagaaggct cccacttgag 1380
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tttggttttg tttgggttg gtgggtcatt gcggtcttag attatgtttc tcttgetacc 1560
aaacagtcac gtattaactc tctttggatg atgaagtta aagagtcaat aaatagaaac 1620
accagatgac tgcaaaaaaa aaaaaaaaaa aaaaaaana aaanaaaaaa aaaaanaaaa 1680
aaaaaaaaaa 1690

<210> 114
<211> 620
<212> DNA
<213> Homo sapiens

<400> 114
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ttgtaagggg ccatagcctc ttcaggacca actggaggga gagttaggaa acaccagctc 180
ctgcctgggg cagtgaaggga atgggagcag ctgtggggcg ctcatttcag gcaagtcctc 240
cccaaacctt cagatgcagt gagacctggc ctctctgttg tgcttttcag actttgtttt 300
cagaatgctt ttatctcgag tgtgcccttc ggccctcaca agagcccctg gggagtaggt 360
ggtggcctgt gccgtcatcc ccatttcaaa gcagggagct gaggtcctgg gaggggaaag 420
tgcttgccctg aggtcccact gtgttagtgg gtgggcagga ctggaactcg gttctccaac 480
agcccagagc tcactctttt acaccagag gtggagcagg tggcttaggg ggtggttatg 540
tacttcacaa gccaatccc ttcagccagg agctcctggg tgcatttcg tgtcagaaac 600
agtaccgagt cccacccct 620

<210> 115
<211> 542
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (392)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (412)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (511)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (521)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (535)
<223> n equals a,t,g, or c

<400> 115
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cctctactcc agcctccact ccggcctcca ccatgtccgt cagggtgacct agaagtccta 120
caaggtgtcc acctccggcc cccgggcctt cagcagccgc tcctacacca gcgggcctgg 180
ctcccgcatc agctcgtccg ccttctcccg ggtgggcggc asttccgggg gggcctgaac 240
agcagcatga gtgtggtcgg gggctacggc ggcggggccg gggatgagg ggcacacgg 300
ccgtctcagt gaaccagagc ctgctgagcc cccttwaagc tggaatkagg tcccaacatc 360

caagctgtgc gcaacccagg agaaggagca gntcaagacc ttcaacaaca anttggcttc 420
gttcatcgac aagtgaagca ctggagcagc agaacaaatt tttggagacc aattggagct 480
tcttaaagca gcagaagacg cgcggagaac ntagacaaat ntctgagagt aaatnagaac 540
tt 542

<210> 116
<211> 525
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (420)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (424)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (517)
<223> n equals a,t,g, or c

<400> 116
aattcaaccg tcgttatccc aaaattcagt ttctactttc caccggccct tccggcacta 60
tgctggatgg tgtactggag ggaaaactga atgcggcggt tattgatgga cccattaacc 120
atactgccat cgacgggata ccggtatacc gcgaggaact gatgatcgtc acgccacaag 180
gatatgcgcc agtaaccctt gccagtcagg ttaatggcag taacatttat gccttccgcg 240
ccaattgttc gtatcgtcgc cacttcgaga gctggtttca tgctgacggt gccgctccgg 300
gaactatcca tgagatggag tcttatcacg gaatgttggc ctgtgtgac gcaggagcag 360
gcattgcgtt tattccgcgc tctatgctgg aaagtatgcc ggggcatcac cargttgaan 420
cgknggccgt tagctgagca atggcggtgg ttaacaacct ggctggtctg gccgtcgtgg 480
tgcgaaaaaa cgttccgctc gaaggggggc ccggtancca attcg 525

<210> 117
<211> 728
<212> DNA
<213> Homo sapiens

<400> 117
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gcggcggcct cctggagaat gccaaacccc tcatctacca gcgctctggg gagcggcctg 120
tgacggcagg cgaggaggac gagcagggtc ccgacagcat cgacgcacgc gagatcttcg 180
atctgattcg ctccatcaat gacccggagc atccactgac gctagaggag ttgaacgtag 240
tagagcagggt gcgggttcag gttagcgacc ccgagagtac agtggctgtg gctttcacac 300
caaccattcc gcactgcagc atggccaccc ttattggtct gtccatcaag gtcaagcttc 360
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cagagcatgc agtgaacaag caacttgacg ataaggagcg ggtggcagct gccctggaga 480
acaccacact cttggagggt gtgaatcagt gcctgtcagc ccgtccctga gccctggcctt 540

tgacccctca gcctgcatac tggatctctg gtcccagctc ctgccagggc tgttaccgtt 600
gttttcttga atcactcaca atgagaaact aacattttgc tttttgtaat aaagttaatt 660
tatattcarw tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa acccgggggg 720
gggcccccc 728

<210> 118

<211> 948

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (920)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (944)

<223> n equals a,t,g, or c

<400> 118

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agcagaagag gaagcctggg ctgcggcgga gcccatcaag aaagtccgga agtctctggc 180
tcttgacatt gtgatgagg atgtgaagct gatgatgtcc aactgcccga agtctctatc 240
cttgccgaca actgcccctt caaactcttc cagcctcacc ctgtcaggta tcaaagaaga 300
caacagcttg ctcaaccagg gcttcttgca ggccaagccc gagaaggcag cagtggccca 360
gaagccccga agccacttca cgacacctgc ccctatgtcc agtgccctga agacggtggc 420
ctgcgggggg accagggacc agcttttcat gcaggagaaa gcccggcagc tcctggggcg 480
cctgaagccc agccacacat ctgcggacct catctgtcc tgagggtgtg aggggtgtcac 540
gagcccatc tcatgtttac aggggttgtg ggggcagagg ggggtctgtg atctgagagt 600
cattcagggtg acctcctgca gggagccttc tgccaccagc cctccccag actctcaggt 660
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cgtcagcttc tcccagccc acgtcaggcc tggcctcacc tcagaccctg cttaggatgg 840
gggatgtggc caggggtgct cctgtgtctc ccctctcttg gtgcattttt ttggaagaat 900
aaaattgcct ctctcttgn aaaaaaaaaa aaaaaaaaaa gggnggcc 948

<210> 119

<211> 211

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (123)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (125)

<223> n equals a,t,g, or c

<400> 119

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tcgaccacg cggtccgctt ggtggggtcg gctgctttct cgcgtttccc cccaaccccg 60
tccggcctcg cccagcgctt ccacgcggaa ccaactgcca gaggcgcggc gcggcgtcga 120
gcngngcgag tgtgaggaaa ccgccgcctc agccgagcgc gcgggcccgcc ccagggcgctt 180
agttttcggc gcgcagtcgc ggtcccccg c 211
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<210> 120

<211> 1308

<212> DNA

<213> Homo sapiens

<400> 120

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gtttggacat gagctgaggg cacggtcgcg ggcggtcagc ctggttcgcag ctacggcgag 180
gaggggcgcg attgtyoctt gttgccgctc cgttagtggt ccgcgtccat tccgcgcggt 240
gtcccgattt taggggtagg gagaagtgtc agcttcaggc atcgcgaggc gtggcgggcc 300
catggccccg ctgggaggcg ccccgcggtt ggtactgctg ttcagcggca agaggaaatc 360
cggaaggac ttcgtgaccg aggcgtgcga gacgagactt ggagctgatg tctgtgctgt 420
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gagactcctg gacaccagca cctacaagga ggcctttcgg aaggacatga tccgctgggg 540
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gcggggctgg gtgttcacgc caggggtgga cgatgctgag tcagaatgtg gcctggacaa 780
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ctggccgagg tgaggaacag acaggggggg tctagattct gagggggtt gtggatattg 1020
ggcaaggcag gaaacctctg gagacctcat tttctccatg gggaagacag ccatgctctt 1080
caggaggaga ctccaagggc aaaggagggt gtcttggtg tgcttgaagg cgaaaccctg 1140
ccatatcccc agtgccagtc ccctcagcct gtggtggcct tgcactctga ctggatgttc 1200
tcagcccctt gttctgggca agaaccaga gctccccagt gtggatacta ataaacctct 1260
tggagcacia aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaagg 1308
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<210> 121

<211> 2516

<212> DNA

<213> Homo sapiens

<400> 121

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ctattgaaat cacaaaagta gaacagggcw ytttattttt gtataattta ggattaggta 180
tgcttctttg ttctaacaag tcatgttttc taacccttct ttcactaagc aaaccagAAC 240
agatttgaac tgttatgggt tataatattag tatggagatc agctcagatg acattaaaaa 300
tgccgtagtg ttattcttgt atgccaaatc tttttttccc caaaattagc actttaattt 360
tatttactgt tataatattt gttttcttag attaggtagg aaatcttaat ttggccaccg 420
cctactttga caagtaata ttacatcata cgattttgca acattaaatt agaacactag 480
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aaactaaaaa attatgtttc agtgaatgct acaactaagc attttttttt tttaagaaaa 540
acaattgtat tatgttttgt tgccttgcca ctttgagtat cttatctgaa aatctgttcc 600
ttgccatgtt tttctcctgt taacataaac tatgtgccct gtgaatttct ggggactgaa 660
tttgaaattg ctccctgcaa ccqtttttqg cctggcgtgt atctgaatgc ctgaatatct 720
ccccgctgaa tgaatttcgt attctgccct gaattcactc gggatatattg attggctgga 780
tgatccttggg gccgccact tgacgtttcc agaagagtca ccgaagaaaa gaaccaggag 840
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atgtatagaa tttttttcaa cacttattaa cttttcagat aacataatct atatatagat 960
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tccatttctt ttgggtgggg ggattgtatt tttgctttct ttagaaatgt aatgtttgtt 1080
atatagaact tccagaacag taatcaaatt aatgaaatta gacctataa ttatgttttt 1140
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<210> 122

<211> 1139

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1053)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1124)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (1125)
<223> n equals a,t,g, or c

<400> 122

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gcaaggagct gtttccatt cagatggagg gtgtcaagct cacagtcaac aaagggttga 480
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ccagcacaag gwtgcaggac accagcgtct ccnttsggg accagcttgg aacttgccca 1080
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<210> 123
<211> 2114
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1966)
<223> n equals a,t,g, or c

<220> .
<221> misc feature
<222> (2039)
<223> n equals a,t,g, or c

<400> 123

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gcgcccagcc aagcgatctg gagagcgcg ggcgtgtgca tgagattttc acgtcgccgc 180
tcaacctgct gctgcttggc ctctgcatct tcctgctcta caagatcgtg cgcggggacc 240
agccggcgcc cagcgcgac agcagcagc acgagccgcc ccctctgcc cgctcaagc 300
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<210> 124

<211> 583

<212> DNA

<213> Homo sapiens

<400> 124

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<210> 125

<211> 1987

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

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<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (14)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (517)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1960)
<223> n equals a,t,g, or c

<400> 125
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cggtgat 1987

<210> 126
<211> 1451
<212> DNA
<213> Homo sapiens

<400> 126
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aaaaaaaaa a 1451

<210> 127
<211> 1234
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (857)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1204)
<223> n equals a,t,g, or c

<220>

<221> misc feature
 <222> (1226)
 <223> n equals a,t,g, or c

<400> 127

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<210> 128
 <211> 863
 <212> DNA
 <213> Homo sapiens

<220>
 <221> misc feature
 <222> (840)
 <223> n equals a,t,g, or c

<400> 128

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tctcctgggg ctggaagtgc caaagcctg ggcaaagctg tgtttcagcc acactgaacc 780

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aaaaaaaaaa aaaaagggcg gcc 863

<210> 129

<211> 1238

<212> DNA

<213> Homo sapiens

<400> 129

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<210> 130

<211> 379

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (373)

<223> n equals a,t,g, or c

<400> 130

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<210> 131

<211> 1786

<212> DNA

<213> Homo sapiens

<400> 131

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<210> 132

<211> 974

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (165)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (853)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (963)

<223> n equals a,t,g, or c

<400> 132

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974

<210> 133

<211> 634

<212> DNA

<213> Homo sapiens

<400> 133

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634

<210> 134

<211> 1855

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1818)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1845)

<223> n equals a,t,g, or c

<400> 134

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cgcgcgcagg ccggcctctg tgtgtgcgcc acagcgagcc ggtgtgcggc agcgacgcca 180
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<210> 135

<211> 917

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (913)

<223> n equals a,t,g, or c

<400> 135

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tgccctgagc tcggcgggct ggcattcggc ccggggaaaa gcggagcagg tctgcgaggc 240
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<210> 136

<211> 1271

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1236)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1255)

<223> n equals a,t,g, or c

<400> 136

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atccgcgggc tggcccaykc catccgcctg ctccctggaat acacagactc aagctaygag 180
gaaaagaagt acacgatggg ggacgctcct gattatgaca gaagccagtg gctgaatgaa 240
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atcacccaga gcaacgccat cctgcggtac attgcccgca agcacaacct gtgcggggaa 360
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cagctggcca aactctgcta tgaccagat tttgagaaac tgaaccaga atacctgcag 480
gcactccctg aaatgctgaa gctctactca cagtttctgg ggaagcagcc atggtttctt 540
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<210> 137

<211> 2017

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (295)

<223> n equals a,t,g, or c

<400> 137

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aacaggagat tgctactcta gacaacaaga caatgactga tgtggtgggt aaccararga 180
rgagcgccga gctgagttct acttccagcc ctgggkcagg aggctgtgtg ccratacttc 240
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<210> 138

<211> 937
<212> DNA
<213> Homo sapiens

<400> 138
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<210> 139
<211> 2759.
<212> DNA.
<213> Homo sapiens

<220>
<221> misc feature
<222> (171)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1654)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2743)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2744)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2746)
<223> n equals a,t,g, or c

<400> 139

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<210> 140

<211> 1241

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<400> 140
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa g 1241

<210> 141
<211> 3405
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1569)
<223> n equals a,t,g, or c

<400> 141
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tttgtcacgt gtgtccggca gccagaatc cgagccgtgc taggagaagt ggtctctatc 120
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<211> 2268

<212> DNA

<213> Homo sapiens

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<222> (2169)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2196)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2232)

<223> n equals a,t,g, or c

<400> 142

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gaattatgac tncattatga aaaaaagaag ttttaaagtt ttcaatac 2268

<210> 143

<211> 1757

<212> DNA

<213> Homo sapiens

<400> 143

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attttcacac acagtgtgta agatgtgca agaccaaatac atagctcata aaatcagggtc 180
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ggcattgttt ctgtctcatg agaattcttt tattcattac cataagcctt cactgatact 660
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aaaaaaaaaa aaaaatt 1757

<210> 144

<211> 1062

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (52)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1056)

<223> n equals a,t,g, or c

<400> 144

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<210> 145

<211> 1030

<212> DNA

<213> Homo sapiens

<400> 145

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catctgcaca ggcgctcgac agctccaaga cgtgcggcc aagcagaaag ttgaacagaa 180
cgcggtccc agccacacca agttcagcat ttaccctccc attccaggag aggagagctc 240
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III

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1030

<210> 146

<211> 814

<212> DNA

<213> Homo sapiens

<400> 146

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<210> 147

<211> 2678

<212> DNA

<213> Homo sapiens

<400> 147

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<210> 148

<211> 1028

<212> DNA

<213> Homo sapiens

<400> 148

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<210> 149

<211> 1425

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (647)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1359)

<223> n equals a,t,g, or c

<400> 149

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cccggtgtg cagatgatgg ggggtttgca tatttgcang ggactagcga gtcaggcagg 1380
aggtttgcac atgtgaatat agaactccgc agccctcat gagca 1425
```

<210> 150

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<400> 150

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gctgcgagaa gacgacagaa ggggagagcc aatggaaagg ggctgccgcg cggccgtaaa 60
```

gagttttag agcagttcgg gtgcggtacg ttgcattccg gtaccggacg ccgagagcgg 120
ttgtctccg tctctggagt tgtaggcgag aggtgatcat gtccggtcgc gggaaacagg 180
gcggcaaaagt gcgagcaaaag gccaaatccc gtcctcccg cgcgggcctg cagttcccgg 240
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ccgcaacgac gaggagttaa acaagctgct gggcaaaagt accatcgctc agggcggcgt 480
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gaggtgggag gcgagggtcc cggcgggagc caataaagtt ggtgaaaatc gtaaaaaaaa 720
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 780

<210> 151

<211> 1066

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1061)

<223> n equals a,t,g, or c

<400> 151

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tacgagacct tgacgcggcc gttctctgga cgcgggctgc cggctccggc ctgggcccga 180
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cgcctggtca cgcgcaagtc ctggtgtgg cagcagcagc agccgtgcta ctggcgctc 300
acgcgggtgc ggcccgacta cacggcgag aacttgacc acgggaaggc ctggggcatc 360
ctgaccttca aagacgcctc tttttcttca tcagggaaga ctgagagcga aggcgcggga 420
gatcgaacac gtcattgacc atgactggcg gctggtgccc aagcacgag aggagccctt 480
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gctgaatgtg cagaggatac gcatggaacc ctgggattac cctgcaaac aggaagacaa 660
aggaagggcc aagggcaccc ccgtctagaa tgccagaacc agcgggtggc cttaggggct 720
gtgaggcagt ggggacctta ttgatgaaag aaaccgtctt tgcgttacac ccgagtcctg 780
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tccgagggcc cagctgggg aaagcgggaa gcgctcgctc cctttccccc attagtgtc 960
tctctgcctg gatcccgga gaagctatga aagggaataa agagaaaaga artamaaaaa 1020
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa ncccct 1066

<210> 152

<211> 1649

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1543)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1579)

<223> n equals a,t,g, or c

<400> 152

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accccggtc tcgaaggagg tgtgacatca tcatcatctc tggccggaaa gaaaagtgtg 60
aggctgccaa ggaagctctg gaggcattgg ttcctgtcac cattgaagta gaggtgccct 120
ttgaccttca ccgttacgtt attgggcaga aaggaagtgg gatccgcaag atgatggatg 180
agtttgaggt gaacatacat gtcccgccac ctgagctgca gtctgacatc atcgccatca 240
cgggcctcgc tgcaaatttg gaccgggcca aggctggact gctggagcgt gtgaaggagc 300
tacaggccga gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc 360
ccaaatacca tccaagatt atcgggagaa agggggcagt aattacccaa atccggttg 420
agcatgacgt gaacatccag tttcctgata aggacgatgg gaaccagccc caggacccaa 480
ttaccatcac agggtagcaa aagaacacag aagctgccag ggatgctata ctgagaattg 540
tgggtgaact tgagcagatg gtttctgagg acgtcccgtt ggaccaccgc gttcacgccc 600
gcatcattgg tgcccgcggc aaagccattc gcaaaatcat ggacgaattc aaggtggaca 660
ttcgcttccc acagagcggg gccccagacc ccaactgcgt cactgtgacg gggctcccag 720
agaatgtgga ggaagccatc gaccacatcc tcaatctgga ggaggaatac ctagctgacg 780
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gaagacctgg caatggacag caggaggcag gttcctggag ctnggggggtg acctgagagg 1560
cagaggttga cgggttctna ggcagtcctg attttacctg ccgtggggtc tgaaarcacc 1620
aagggtccct gaccctacct ccaactgcca 1649
```

<210> 153

<211> 660

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (35)

<223> n equals a,t,g, or c

<400> 153

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ccggaaattc ccgggtcgac ccacgcgkcc gcggagwgc tcacacgtgt gctccctgcc 60
ctgctcctgg ccccttgccc ggccgggctg tttctggcca tgggtcgctc ccgcccggaca 120
ggcgcgcacc gagcgactc tctagcccgg cagatgaagg cgaacggcgg cggccggact 180
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tggatgagat tcaccgcgag ctgcggcctc agggatccgc acgaccccag cccgacccaa 240
acgccgagtt cgaccccgcac ctgccagggg gcggtctgca ccgctgtctg gcctgcgcga 300
ggtacttcat cgattccacc aacctgaaga cccacttccg atccaaagac cacaagaaaa 360
ggctgaagca gctgagcgtc gaqccctaca gtcaggaaga ggcggagagg gcagcgggta 420
tgggatacta tgtgcccccc aggcggctgg cagtgtccac ggaagtgtcc actgaggtcc 480
ctgagatgga tacctctacc tgacatggcc tgaagatgca gggcagagga attgcccattg 540
gacagtgcag caaggactag gctgggaggg agcgtgccaa ccccttttgc ctctgggttt 600
ggggagcggg gggcctcttc ttggtgccct gccccaata aaggaactgg acaaagagaa 660

<210> 154

<211> 605

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (449)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (574)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (578)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (583)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (587)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (596)

<223> n equals a,t,g, or c

<400> 154

ggcagagctc caccttccat ccggcgccgg ctttcggcgc gacggtcgcc gcgttccatc 60
gtcgcgcggc ccttcggggc cccgagcccg caatgtcggg ccccaacgga gacctgggga 120
tgcgggtgga ggcgggagcg gaaggcgagg aggacggctt cggggaagca gaatacgtg 180
ccatcaactc catgctggac cagatcaact cctgtctgga ccacctggag gagaagaatg 240
accacctcca cgcccgctc caggagctgc tggagtccaa ccggcagaca cgcctggagt 300
tccagcagca gctcggggag gcccccagtg atgccagccc ctaggctcca agagccccc 360

accgggaccc aacctgcct ccctgggcta ggctctggcc tgggcactca mccccctggct 420
tagacamctt ctcaagggct ggccctcang gacctctggg gggctctgct gcctgggcca 480
accttctctgc ctgggscctc ccttggctam ctgggscagc ccccaaccaac tggcatgccc 540
tcctgggggc caaagaatgg ggctgcaac ccancantt gcntgcnaa cccaanttcc 600
tgggg 605

<210> 155

<211> 695

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (173)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (499)

<223> n equals a,t,g, or c

<400> 155

gaaccctaga aaaaaggatg cagtactaaa gtgtcattca ttcaaagcca ctctctctttt 60
ggtattccac ccattttcca gacggtgaca ctgaggctca ggaagcagta gggacttgca 120
caaagccctt tgggaagcag gctgggaaac agtggaggga ggggtgtccat tanccecaag 180
gagacacagg atctgggctc tktytttsgc ctctctccca gaatacgtg ccatcaactc 240
catgctggac cagatcaact cctgtytgga ccacctggag gagaagaatg accacctcca 300
cgcccgctc caggagctgc tggagtccaa ccggcagaca cgcttgaggt tccagcagca 360
gctcggggag gccccagtg atgccagccc ctaggctcca agagccccc accgggaccc 420
aacctgcct ccctgggcta ggctctggcc tgggcactca cccccctggct tagacacctt 480
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ctgggrcctc cccttggtcc tactggggcc agccccacc acctggcatg ccctctctggg 600
gccaaagatg ggctgcaam ccaccattg ctgcccac caattcctgg gcgytcccca 660
wtytgcccag gcttgaatgt tcacatgaaa tgggt 695

<210> 156

<211> 780

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<400> 156

cggtgggctc gcgttgaggc tgcggctcatg gagggagcag gagctggatc cggcttccgg 60
aaggagctgg tgagcaggct gctgcacctg cacttcaagg atgacaagac caaagtgagc 120
ggggagcgcg tgacgtcat ggtggagttg ctgaaggtct tggttgtgga agcagcagtc 180
cgcgccgtgc ggcaggccca ggcagaagac gcgctccgtg tggacgtgga ccagctggag 240
aagggtgctc gcagctgctc tggacttcta gggatctcag ccgtggckna ggccaccccc 300

agaggagccc ctggtccaca gaagcaggcc ttgtgtttcc agcggcctct gataagaggc 360
aggggaaggam ctgaaggatt tggarttgat tcaaacaaga tctctgggag tctccagcct 420
gtgcagaagg ggcaggactg cagtgcactg cgggccttgg agtgtccagt ggggacactg 480
gtgtgggaag gggcagcacc tggggagtcn ctgctctcc tccctgggac aataglytyc 540
atgccacccg ggttcctaca ggcagggtgt gggaaaggcc tggccagcag gtagcctgtg 600
tgtttgacaa acagcagctg gcagcgctgc ctccctgcca cattcctgcc acccgacatc 660
aaagctggcg tgtgaccttt ccagccatgc gatattcccc ttggaagatg cttccccagg 720
ctataaattt gttctcacia agcaacatca ataaatcaaa actgtctcty ccaaaaaaaaa 780

<210> 157

<211> 1127

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1113)

<223> n equals a,t,g, or c

<400> 157

aacttcagt ccctcactgt agaatttaaa agccttactg ttgattgccc atgggtggact 60
tgatggagaa attaaatatt ttccattatg ctttcaaaaa tactgtatat gtttcagcaa 120
gtttggggaa tgggagagga caaaaaaaag ttacatttaa tctatgcatt tttgccaagc 180
catattgagt tattttacta ctagagacat taggaaacta actgtacaaa agaaccaagt 240
ttaaaagcat tttgtggggt acatcatttc tataattgta taatgtatgt ctttgtgggt 300
ttaaatgata aagacattaa gttaacaaac atataagaaa tgtatgcact gtttgaaatg 360
taaattattc ttagaacact ttcaatgggg gttgcattgt ctttttagtg ccttaatttg 420
agataattat tttactgcca tgagtaagta tagaaatttc aaaaaatgta ttttcaaaaa 480
attatgtgtg tcagtgaagt ttccattgat aattggttta atttaaaata tttagaggtt 540
tggttgactt tcataaattg agtacaatct ttgcatcaaa ctacctgcta caataatgac 600
tttataaaac tgcaaaaaat gtagaaggtt gcaccaacat aaaaaggaaa tatggcaata 660
catccatgat gttttccagt taacatagga attaccagat aaatactgtt aaactcttgt 720
ccagtaacaa gagttgattc atatggacag tatgatttat tgtttatttt ttttaacaaa 780
tacctcctca gtaatttata atggctttgc agtaatgtgt atcagataag aagcactgga 840
aaaccgatcg tctctaggat gatatgcag tttcaagtgg tattgaaagc cgcactgatg 900
gatatgtaat aataaacata tctgttatta atataactaat gactctgtgc tcatttaatg 960
agaaataaaa gtaatttatg gatgggtatc ttttaatttt actgcaatgt gttttctcat 1020
ggctgaaatg aatggaaaac atacttyaat tagtctctga ttgtatatata atgtttgtga 1080
aattccatgg ttagattaaa gtgtrttggg aanaattctc catggggg 1127

<210> 158

<211> 1282

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (120)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (205)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (207)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (732)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1279)
<223> n equals a,t,g, or c

<400> 158
tgctctacaa atagtataaaa taaaaaataa aaaaagtagc tgggcgtggt ggtgtgcacc 60
tgtgtgccca gctgcttggg atgctgaggt ggaaggatct cttaaaccce ggaggggtggn 120
aggctgcagt gaacttgcca ttgcaaccact ggcactccag tctgggggac agagtgcagac 180
cccatctcaa aaaagtgttt aattnantat acttggtgagt ggtctatttg catttnaaaa 240
ctgctttcta gaattaggat agctccctta ggtttaatgt tttggtgagc aggaatatca 300
gttacccttc cagatcttaa ttctagtttt tttatcactt tttcatgagg tgatctcatc 360
ctcatctcct agcatgtctg gcaattttga tttctgaact ctgtgctacc tcagaggcca 420
gcttccttag ggaaaaatca gtgctgaaat aaagttatat ttccttttct gctctaaata 480
tatagtgggg gaataagaga aatgaagagg aattcctgag aacgtaatta ctagaacttc 540
ccctctccca cgtaatgtct ctacacacac atggaccctt attcccccac tttgcgaccc 600
cccacccac ccacaacag gtggtgatct ttgtgaagtc tgtgcagcgg tgcattgcct 660
tggcccagct actagtggag cagaacttcc cagccattgc catccaccgt gggatgcccc 720
aggaggagag gntttaaaga ttttcaacga cgaattcttg tggctaccaa cctatttggc 780
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aactaaaaat gaaacacatg tgtctgtggt atctaaaaaa aaaaaaaaaa aaawwggggg 1260
ggsqcccgtc cccattggnc ct 1282

<210> 159
<211> 1505
<212> DNA

<213> Homo sapiens

<400> 159

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atcaggcatg agtgaccagt tgtgtggcat tgetgcctgc cagacggatg acatatacaa 120
ccgaaactgc cttattgaat tggtaacct gtcagatggt tcttcgtgga gcagagacak 180
aaggctgtgt catttgtgtca gctgccaaag cccaactgct gcagtgccag caccatccag 240
cctggtatgg tgatacattg aagcaaaaga catcctggac ttgcctcttg gatggcatgc 300
agtactttgc caccactgaa agcagcccca cagagcagga tggccgacag ctctggttag 360
aggtgaagaa tatcgaggag caccggcagc gtagtctgga ctctgtgcag gagctgatgg 420
agagtgggca ggcagtgggc ggcagtgtta ccacaaccac agattggaac cagccagctg 480
aggcagacga agcccagcaa gtccagcgga tcatttcgag ttgcaactgc cgaatgtact 540
atattagtta cagccatgac attgatcctg aactagcaac tcagattaag ccacctgaag 600
ttcttgagaa ccaggaaaag gaagatctcc taaagaagca ggaaggggct gtggatacct 660
tcaccttat ccaccatgag ctggaaattt ccaccaacc agctcagtat gccatgatcc 720
tgacattgt caacaacctg ctgctccatg tagaacctaa gcggaaggaa catagtgaga 780
agaagcaacg ggtcagggtt cagcttgaga tctctagcaa tccagaggag caacgcagca 840
gcatactgca tttgcaggag gctgtgcggc agcatgtggc ccaaatacga cagctggaga 900
agcagatgta ttctatcatg aagtctttgc aggatgacag caagaatgag aatctgcttg 960
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tgctcaggca cggtggcgcc tgacagagga agatggacag ctgggaattg ctgaattaga 1200
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gcggccccag agctcctgcc agtctggcg acagctagct ctccgcctct tcagcaaagt 1380
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accatccagc tgacacacca ttcttcaca gatgatgggc tttctttcc tggccgaagt 1500
gtgga 1505
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<210> 160

<211> 736

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (718)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (723)

<223> n equals a,t,g, or c

<400> 160

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aggcagcagg gacacttggg gtctggacgc aacggcgggc ggagcatgaa cgcccctcca 60
gccttcgagt cgttcttgct cttcgagggc gagaagatca ccattaacaa ggacaccaag 120
gtacccaatg cctgtttatt caccatcaac aaagaagacc acacactggg aaacatcatt 180
aatcacgtg cctgcttccc ctgcgcttc tgccgtgatt gtcagtttcc tgaggcctcc 240
ccagccacgc ttcctgtaca gcctgcagaa ctgtgagtca attaaacctc ttttcttcat 300
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aaattacca gttctcata gttctttata gcagtgtgaa aacagactaa tggacccttc 360
tgggtgaagg aatgcagcca ttctgcttgt ttgactatgt cctttctatt catctctatt 420
tcctgggagg tgtttatcca agtgcaatag gaggtattgg tgaccgcaca gtcccctcag 480
tgttctgcta gtaaatagtt gaaggttgat cattgatctt ctgcgttttc agtctggcat 540
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gtccaggctt gtcttgcaac tgtatgttct cttcagacct ctccctggcg atgccagatt 660
cactgggctg gcagattctg ccccccccaa aaaaaaaaaa aaaatattaa taataaanaa 720
aanagactcc caggga 736

<210> 161

<211> 995

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (59)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (889)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (899)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (928)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (933)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (938)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (974)

<223> n equals a,t,g, or c

<400> 161

gggtcgaccc acgcgtccgg gcggcctcgg cagcgggtgtt ctcgcgttg cgaasgggnc 60

tccggctcgg ctgcgaggga ctgtgcacga ggttggcgac gcgccccgcc gggccccaga 120
tcaggccgca gagatcggga gccgcgggag cactaaggcg caagggccac agcagcagcc 180
gggctcagag ggtccagct atgccccaaa agttgcgctc tggcttgctg ggctgcttgg 240
agctggtggg actgtgagcg tcgtctatat ctttggaaac aacccgggtg acgaaaatgg 300
tgccaagatt cctgatgagt tcgacaatga tccaattctg gtacagcagt tgcgccggac 360
atacaaatat ttcaaagatt atagacagat gatcatcgag cccaccagcc cttgccttct 420
cccagacctt ctgcaggaaac cgtactacca gccaccctac acgctcgttt tggagctcac 480
cggcgctcctc ttgcatcctg agtggctcgt gccactggc tggaggttta agaagcgccc 540
aggcatcgag accttgttcc agcagcttgc ccctttatat gaaattgtca tctttacgtc 600
agagactggc atgactgcgt ttccactcat tgatagtgtg gacccccatg gcttcattctc 660
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cctgcagccc tataacggcg ttgcctgcg gccctgggac ggcaactctg atgaccgggt 840
cttgttggat ctgtctgcct tcctcaagac cattgcactg aatggtgtng gaggacgtng 900
cgaaccgtgc tgggagcatt atgccctngg ganggatnga ccccgctggg cggcttttyc 960
aaacagcggc aaancgggct tagaagcagg gagga 995

<210> 162

<211> 1125

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (972)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1023)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1077)

<223> n equals a,t,g, or c

<400> 162

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cgctgcagga cgagacctg ggtgtggcgt ccgtgccctc gcagtggagg gccgtccagg 180
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tgaactggac cgagcagcag cagatggtgt cttgtctgta taccctgggc taccgcag 480
ccaagcgca ggtctgcat gtgaccagca tctcctggaa ctccactggc tctgtggtgg 540
cctgtgccta cggccggctg gaccatgggg actggagcac gcttaagtcc ttcgtgtgtg 600
cctggaacct ggaccggcga gacctgcgtc cccagcaacc gtcggccgtg gtggaggtcc 660
ccagcgtgt cctgtgtctg gccttcacc ccacgcagcc ctcccamgtc gcaggagggc 720
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gcacaggcct gacggatgac acccacacag accctgtgtc ccaggtggtg tggctgccc 840
agcctgggca cagccamcgg ttcaggtgc tkagtgtggc cacygacggg aaggtgtac 900
tctggcargg catcggggta rgccagctgc agttcacaga rggttcgcc tggttcatkc 960
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canggcaggc tttcttcag tttgacctca ggttttcatt ttggcaggaa gcggttnccc 1080
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<210> 163

<211> 423

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (390)

<223> n equals a,t,g, or c

<400> 163

gggtcgaccc acgcgtccga gatggcggtt cgcagcaaga ggccggagca cggcgggccc 60
ccggagctgt tttatgacaa gaatgaagcc cggaaatacg tgcgcaactc acggatgatt 120
gatgtccaga ccaaaatggc tgggcgagct ttggagctcc tttgtctgcc ggaggtcagc 180
cctgttacct cttgatatt ggctgtggtt ctgggctgag tggagattat ctctcgatg 240
aagggcacta ctgggtaggc atcgacatca gccctgccat gctggatgag gccttggacc 300
gagacactga gggagacctg cttctggggg acatgggcca gggcatcccc ttcaaaccag 360
kttcattgat ggatgtatca gcattctgcn aatcagtggc tctgtaatgc aaaccaagaa 420
gtc 423

<210> 164

<211> 1642

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1614)

<223> n equals a,t,g, or c

<400> 164

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gcctccccca ccaccacagc cccccaccca tcaagcttca gtcgggctgc tggacacccc 120
tcggagccgt gagegctcac catccctctt gcgsggcaac gtggtcccaa gccactgcc 180
cactcgccgg acgaggacct tctcgcgagc ggtgcgggct tcacagggcc ccgtctacaa 240
aggagtctgc aaatgcttct gccggtccaa gggccatggc ttcattaccc cagctgatgg 300
cggccccgac atcttctgac acatctctga tgtggaaggg gagtatgtcc cagtggagg 360
cgacgagggt acctataaaa tgtgtccat cccaccaag aatgagaagc tgcaggccgt 420
ggaggtcgtc atcactcacc tggcaccagg caccaagcat gagacctggt ctggacatgt 480
catcagctcc taggagatgg tggaaagcacc ccttgcctctg tgcttgggg agactttgag 540
gggaggaggc agcagacact ggagatgaca ttcttcacac cgagacgggg cttcagccgg 600
gcatgggtccc tctcaagtat ctcttgaggg aaggggtatg gggggcagggt gtgggggtgtg 660
gggtgttccc ggcatcagc acagcctatg accattgcaa caacctctca ccatctgaag 720
agcattaaaa gcatttaaaa aggaragggt cccactggtg gctgagtgga ggttccaacc 780

ccatcccagg gagtggatca aggggtggtat ttctccagct gctcagacac atggggtcaa 840
cccacagaat ccctcttctt cctggagctg gagggcccag attcccagat ctggccccct 900
ggcagcctga cagggacctt gcgtgacttc tccaaggcaa atttccacct aagtggcccc 960
tgcgcctctc ctggggcctg ggcaaaqcaq ttttctaatt ctgggcttgg ttgggttctag 1020
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aactaaagct ttcacccaga gccggctctg tttgcacttt gctgccgaca ttgcaaactt 1560
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<210> 165

<211> 1115

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (390)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (394)

<223> n equals a,t,g, or c

<400> 165

aggaaatgcc agtactgcag gggctcccca gggagtatgt gaatgccagg cactgtttgc 60
cgtgccacc ttagtgtcag cccagaatg gctcagtgc ctgttttga ccggaggctg 120
accagtgtgt ggctgtgcc catcaagtgg atggcgtgg agtccattct ccgccggcgg 180
ttcaccacc agagtgatgt gtggagtatt ggtgtgactg tktgggagct gatgactttt 240
ggggccaaac cttacgatgg gatcccagcc cgggaggatc cctgacctgc tggaaaagg 300
ggagcggctg cccagcccc ccatctgcac cattgatgtc tacatgatca tggtaaatg 360
ttggatgatt gactctgaat gtcggccaan attncgggag ttggtgtktg aattctccc 420
catggccagg gacccccagc gctttgtggt catccagaat gaggacttgg gccagccag 480
tcccttggac agcaccttct accgctcact gctggaggac gatgacatgg gggacctggt 540
ggatgctgag gagtatctg taccacagca gggcttcttc tgtccagacc ctgccccggg 600
cgctgggggc atggtccacc acaggcaccg cagctcatct accaggagtg gcgggtggga 660
cctgacacta gggctggaag cykctgaaag aggaggcccc caggtctcca ctggcaccct 720
ccgaagggct ggctccgatg tattttrtgg tgacctggga atgggggag ccaaggggct 780
gcaaagcctc cccacacatg accccagccc tctacagcgg tacagtgagg accccacagt 840
accctgccc tctragactg atggctacgt tgccttctg acctgcagcc cccagcctga 900
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tgctgcccga cctgctggtg ccactctgga aagsgccaag actctctccc cagggaagaa 1020
tggggctcgtc aaagagtttt tgccttggg ggtgccgtgg agaaccgccg gtattgacac 1080
cccaggggag ggagcttgc cttcagcccc acctt 1115

<210> 166
<211> 1066
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (10)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (739)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (968)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1023)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1025)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1042)
<223> n equals a,t,g, or c

<400> 166
gggcacgagn cacctgagcc ccttgtctcg caccggctcc caggagggca cctccatgga 60
gggctcccgc cccgctgccc ctgccagagc caggcaccct caagaccagt ctggtggcta 120
ctccaggcat tgacaagctg accgagaagt cccagggtgc agaggatggc accttgcggt 180
ccctggaacc tgagccccag cagagcttgg aggatggcag cccggctaag ggggagccca 240
gccaggcatg gagggagcag cggcgaccgt ccacctcatc agccagtggg cagtggagcc 300
caacgccaga gtgggtccctc tcctggaagt cgaagctgcc gctgcagacc atcatgaggc 360
tgctgcaggt gctggttccg cagtggagaa gatctgcac gacaagggcc tgacggatga 420
gtctgagatc ctgcggttcc tgacagcatg caccctggtg gggctgctgc ccgtgcccc 480
ccccatctc atcgcaagt accaggccaa ctcgggcact gccatgtggt tccgcaccta 540
catgtggggc gtcactatc tgaggaatgt ggaccccct gtctggtacg acaccgacgt 600
gaagctgttt gagatacagc ggggtgtgag atgaagccga cgaggggctc agtctagggg 660
aaggcagggc cttggtccct gaggttccc ccatccacca ttctgagctt taaattacca 720
cgatcagggc ctggaacang cagagtggcc ctgagtgtca tgccctagag acccctgtgg 780
ccaggacaat gtgaactggc tcagatcccc ctcaaccctc aggctggact cacaggagcc 840

ccatctcttg ggctatgcc caccagagac cactgcccc aacactcgga ctccctcttt 900
aagacctggg ytcagtgtg gccctcagt gccaccact cctgtgtac ccagcccca 960
gaggcagnaa rccaatgggt cactgttgcc cctaaaggg gggttttgaa ccaaggggga 1020
aancnacggg gcctggttcc cntttqaaa ggtttccct gggaaa 1056

<210> 167

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (278)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (564)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (597)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (602)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (635)

<223> n equals a,t,g, or c

<400> 167

gtcgcgagcg ctgccgtcgg gaggcgctcc gaggttcgag gctgtgcccc gcgaccccg 60
cttcggcgct cggctcgcag gatggatccc gtaccggga cagactcggc gccgctggct 120
ggcctggcct ggctcgcggc ctctgcaccc ccgcgcggg gkttcagcg gatctcctgc 180
accgtcgagg gggcaccgcc agctttggca agagcttcgc gcagaaatct ggctacttcc 240
tgtgccttag ttctctgggc agcctagaga acccganga gaacgtggtg gccgatatcc 300
agatcgtggt ggacaagagc cccctgccgc tgggcttctc ccccgctcgc gamcccatgg 360
attccaaggc ctctgtgtcc aagaagaaac gcatgtgtgt gaarctgttg cccctkggar 420
ccamggacac ggctgtgttt gatgtccggc tgagtggaa gaccaagaca gtgcctggat 480
accttcgaat aggggacatg ggcggctttg ccatctggtg caagaaaggc caaggcccg 540
aggccagttg cccaaagccc cgangtcctc agcccgggac atgcaaggc ttctctntgg 600
angcagccag ccagcccaag ttaaggcggg gcctncttgg aagccggaca agcgttc 657

<210> 168

<211> 1026

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1011)

<223> n equals a,t,g, or c

<400> 168

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ggcacgagga gagatggagg ggcggcaggt gctggaggtc aagatgcagg tggagtacat 60
gtcattcagc gcacacgcgg acgccaaggg catcatgcag ctggtgggcc aggcagagcc 120
gkagagcgtg ctgctggtgc atggcgaggc caagaagatg gagttcctga agcagaagat 180
cgagcaggag ctccgggtca actgctacat gccggccaat ggcgagacgg tgacgctgcc 240
cacaagcccc agcatccccg taggcattctc gctggggctg ctgaagcggg agatggcgca 300
ggggtgcttc cctgaggcca agaagcctcg gctcctgcac ggcaccctga tcatgaagga 360
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ccagctgcgc ttcacctgcc gcgtgcacct gcatgacaca cgcaaggagc aggagacggc 480
attgctgctc tacagccacc tcaagagcgt cctgaaggac cactgtgtgc agcacctccc 540
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aggcaccaag gtgctgctgg tctcctggac ctaccaggac gaggagctgg ggagcttcct 660
cacatctctg ctgaagaagg gcctccccca ggccccccagc tgaggccggc aactcaccca 720
gccgccacct ctgccctctc ccagctggac agaccctggg cctgcacttc aggactgtgg 780
gtgccctggg tgaacagacc ctgcaggtcc catccctggg gacagaggcc ttgtgtcacc 840
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tttattcctg gttagggcag gtggtcctag acagcagttt ccagtaaaag ctgaacaaaa 960
aaaaaaaaaa aaaaaattgg gggggggccc gttaccatt tggcctttag ngggggtttt 1020
aaatta 1026
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<210> 169

<211> 774

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (730)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (733)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (754)

<223> n equals a,t,g, or c

<400> 169

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gagatgtgag ggcctttgtc tcatcacatc cgagcacagc tcagcaagat gctcttagct 120
agraaacaga ttttatgtgt taatgttaaa aattttgcag ttatttatct tgtggatatt 180
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acagaagtgc ctgacttcaa caaaatgtat gagttatacg atccatgtac tgtcatgttt 240
ttcttcagga acaagcacat catgattgac ttggggactg gcaacaacaa caagattaac 300
tgggccatgg aggacaagca ggagatggtg gacatcatcg agacggtgta ccgcggggcc 360
cgcaaaargcc gcggcctggt ggtgtccccc aaggactact ccaccaagta ccgctactga 420
ggcgccctca gtctgcgcgg ataaatgtcg tggagccctt tttgtatgga aacgttttaa 480
gctattttaa gcctttggaa aatacaggaa gctccagggc tggagcacct ctgagatgga 540
attgataaca tggctttaac tcaccgaaat aaacaagcac gtggtgagag gacgagcct 600
acttgtttgt tctcaggaaa cttaatgaat agattactga ttttcctagt caaagttaat 660
tcttaccctt ggagtaaaac gaaggtgttt atcctgtgag cctgtgcgtt ttgcatactg 720
ggttggtttn ctngggcttc ggtgacagca tatnccgcga gctgggcttt aaca 774

<210> 170

<211> 402

<212> DNA

<213> Homo sapiens

<400> 170

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ggcgaagggtg gacctgagca cctccaccga ctggaaggag gcgaaatcct ttctgaaggg 120
cctgagtgcac aagcagcggg aggaacatta cttctgcaag gactttgtca ggtgaagaa 180
gatcccgaca tggaaggaga tggcgaaagg ggtggctgtg aaggtggagg agcccaggta 240
taaaaaggac aagcagctca atgagaaaaa ctccctgctc cgacgcgaca tcaccaagct 300
ggaggtggac gccatcgtca acgccgcaa cagctccccg cccccaggga gcctaattaa 360
agatcttcgt tgtggcaaaa aaaaaaaaaa aaaaaaaaaa aa 402

<210> 171

<211> 796

<212> DNA

<213> Homo sapiens

<400> 171

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agatccagct ccgtcctgcc tgcagcagcc caaccctgca caccacccat ggatgtyttc 120
aagaagggtc tctccatcgc caaggagggc gtggtgggtg cgggtgaaaa gaccaagcag 180
ggggtgacgg aagcagctga gaagaccaag gagggggtca tgtatgtggg agccaagacc 240
aaggagaatg ttgtacagag cgtgacctca gtggccgaga agaccaagga gcaggccaac 300
gccgtgagcg aggctgtggt gagcagcgtc aacactgtgg ccaccaagac cgtggaggag 360
gcggagaaca tcgcggtcac ctccgggggtg gtgcgcaagg aggacttgag gccatctgcc 420
ccccaacagg agggtagggc atccaaagag aaagagggaag tggcagagga ggcccagagt 480
gggggagact agagggtac aggccagcgt ggatgacctg aagagcgtc ctctgccttg 540
gacaccatcc cctcctagca caaggagtgc ccgccttgag tgacatgcgg ctgcccacgc 600
tctgcccctc gtctccctgg ccacccttg cctgtccacc tgtgtgtctg caccaacctc 660
actgcccctc ctcgccccc cccaccctct ggtccttctg accccactta tgcgtgtgtg 720
aatttttttt ttaaatagatt ccaataaaaa cttgagccca ctyctaaaaa aaaaaaaaaa 780
aaaaaaaaagg gggccc 796

<210> 172

<211> 478

<212> DNA

<213> Homo sapiens

<400> 172

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ggcatccaaa gagaaagagg aagtggcaga ggaggcccag agtgggggag actagagggc 180
tacaggccag cgtggatgac ctgaagagcg ctctcttgcc ttggacacca tccccctcta 240
gcacaaggag tgcccgctt gagtgacatg cggctgccc cgctcctgcc ctctctccc 300
tggccacct tggcctgtcc acctgtgtg ctgcaccaac ctactgccc tccctcgcc 360
ccaccacccc tctggtcct ctgacccac ttatgtgct gtgaattttt tttttaaatg 420
attccaaata aaacttgagc cactcctaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 478

<210> 173

<211> 656

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (59)

<223> n equals a,t,g, or c

<400> 173

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ctgcccttg gatggggcgc tctgaatgt acgtgggccc cgggtgttac aaggagggtga 120
tcattctaca cctctgccag aagcagggtg ttgagaagat accactgccc ttttttgcca 180
tgtccctgag cctgtccccc gggacccacc tcctggctgt tggctttgct gactgcatgc 240
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tgcacctgtg caggtttaca cctccgcca ggctgctct caccggccgc cgcaacgaga 360
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<210> 174

<211> 1891

<212> DNA

<213> Homo sapiens

<400> 174

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1891

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<210> 175

<211> 2161

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

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<220>

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<222> (2160)

<223> n equals a,t,g, or c

<400> 175

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<211> 2411

<212> DNA

<213> Homo sapiens

<400> 176

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2411

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<211> 1338

<212> DNA

<213> Homo sapiens

<220>

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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1276)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1289)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1326)

<223> n equals a,t,g, or c

<400> 177

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<211> 1614

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<213> Homo sapiens

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<223> n equals a,t,g, or c

<400> 178

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<210> 179

<211> 4292

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (4288)

<223> n equals a,t,g, or c

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aacagtcaaa cttatttttg taatgtatgt tattgtgtga tgcagttttt tgcttctgtc 4200
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aaaaaaaaa aaaaaaaaaa aaaaaanaa aa 4292

<210> 180

<211> 243

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (235)
<223> n equals a,t,g, or c

<400> 180
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ccagagggaa gtgtggtgtg tgggcacaac gggaaacgct aaccaggcac agagctcaac 180
ggagcagaca ctgctgaagc ccaagtgaaga aaccacggcg ctttggcgtg taacntggaa 240
tat 243

<210> 181
<211> 813
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (266)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (723)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (726)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (738)
<223> n equals a,t,g, or c

<400> 181
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aggatgacaa gttcctctcc ttccacatgg agatgggtgt gcatgtggat gcagmccagg 180
ccttctctgct gctctcggac ctgmgtcaga ggccagagtg ggacaagcac taccggagcg 240
tgagctagt gcagcaggta gacranggac gacgcatct accacgtcac cagmcctgmc 300
ctcggaggtc acacaaagcc ccaggacttc gtgacccctg cctcgaggcg gaagccttgt 360
gacaatgggg acccctatgt catcgcgctg aggtcgggtc cgctgcccac acaccgagag 420
acgccagagt acagacgcgg agagaccctc tgctcaggct tctgcctctg gcgcgagggg 480
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gcaatgtgt cctcacagag gcatagtcgc cccagctgg gttgtgctcc actgtgacgg 600
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cagcatggcc tgcctctggg aaggagacaca ggtgtccag agcccctggc acaactgctg 720
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813

<210> 182
<211> 822
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (37)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (49)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (370)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (567)
<223> n equals a,t,g, or c

<400> 182
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ccgcgcctat caataaagtt gtcacttgt tgccggccc ctagmccgaa aggttgcgcg 180
cgcagmccga gaagtctcgc gatagccagc cgcggctgcc cttgcgcttc ccgagctggc 240
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<210> 183
<211> 1095
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1082)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1094)

<223> n equals a,t,g, or c

<400> 183

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cctcacctgtg tccgcgctct tttcgcggat cttcgggaag aagcagatgc ggattctcat 180
ggttggtctg gatgcggctg gcaagaccac aatcctgtac aaactgaagt tgggggagat 240
tgtcaccacc atcccaacca taggcttcaa tgtagaaaca gtggaatata agaactctg 300
tttcacagtc tgggacgtgg gaggccagga caagattcgg cctctgtggc ggcactactt 360
ccagaacact cagggcctca tctttgtggt ggacagtaat gaccgggagc ggggtccaaga 420
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gctgggggcta cagcacttac gcagcgcgac gtggtatgtc caggccacct gtgccacca 600
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1095

<210> 184

<211> 3675

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2204)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3329)

<223> n equals a,t,g, or c

<400> 184

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ccctgcagac cctgcacctg cggagaccca gcgcacccag agcaacctgc ccaccagcct 180
ggaggggtctg agcaacctcg cagacgtgga tctgtcctgc aatgacctga cagggtgccc 240
cgagtgtctg tacacctcc ccagcctgcg ccgcctcaac ctgagcagca accagatcac 300
ggagctgtcc ctgtgcatag accagtgggt gcacgtggaa actctgaacc tgccccgaaa 360
tcagctcacc tctgtccct cagccatttg caagctgagc aagctgaaga agctgtacct 420
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gaattccaac aagctggact ttgacgggct gccctcaggc attggcaagc tcaccaacct 480
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cccaaagctg aggaaacttg tctgaacaa gaaccacctg gtgacctcc cagaagccat 600
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<210> 185

<211> 1040

<212> DNA

<213> Homo sapiens

<400> 185

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 ccacagagcc agtttcttcc aaccaggat acatcccttc ctcagaggct aacaggccaa 240
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 ttctttaaaa gcaacttttg gtcccatga gtccaaggat gatgcagctg ccctgtgact 720
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 aaaaaaaaaa aaaaactcga 1040

<210> 186

<211> 817

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (76)
<223> n equals a,t,g, or c

<400> 186

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cggattaagc ctgatcaaga tgacaacctc ccaaaagcac cgagacttcg tggcagagcc 180
catgggggag aagccagtgg ggagcctggc tgggattggt gaagtcctgg gcaagaagct 240
ggaggaaagg ggttttgaca aggcctatgt tgccttggc cagtttctgg tgctaaagaa 300
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cccgccccca tccctcacc cccacctcac tttcaatccg tttgatacca tttggctcct 720
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tcaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaa 817
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<210> 187
<211> 1080
<212> DNA
<213> Homo sapiens

<400> 187

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cgacctgaac gcaaagtccc tgatggacga gacgcccctt gatgtgtgcg gggacgagga 180
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catcgtgtgg caacagccgc cgcaccag cccggagccg cccgaggaca acgatgaccg 420
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<210> 188
<211> 1286
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (1245)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1254)
<223> n equals a,t,g, or c

<400> 188

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gcaccatgac tctagtgtc ttggtgtata ttcttacata ccttttagtg aaaatcctta 180
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gaaccaggag tcagctgtac tagcaactgc tccaaggata gatgatgaaa tccccctcc 420
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1286

<210> 189
<211> 1738
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1480)
<223> n equals a,t,g, or c

<400> 189

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gtcgtggccc ccatggtgga ccagagcgag ctggcctgga ggctgctgag ccggcgccac 180
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gcctttctgc aggacgagtg ggacctgctc caaagaatga ttttgctggc ccacgagaaa 480
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<210> 190

<211> 1923

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1829)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1875)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1910)

<223> n equals a,t,g, or c

<400> 190

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atgaccgctt ccacgagatg cacgtggctc tggcccagaa ggaccaggag atcgcttcc 180
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accagggccc tgtgtggtgt ctctgcgtct actccatggg tgacctgctc ttcagtggct 480
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tccggggcca tgacaacccg gtgtgcacgc tgggtctctc acacaacgtg ctcttcagcg 720
gctccctgaa ggccatcaag gtctgggaca tcgtgggcac tgagctgaag ttgaagaagg 780
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ccgtggctgc ctgctacatg cctgcttnc acgtggctgc acgctgacac acccacattc 1860
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agc 1923

<210> 191
<211> 250
<212> DNA
<213> Homo sapiens

<400> 191
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tcagtgtttt tacatttggt ttttctttta tgctagttgg aaatggagga tgaarataca 180
attgrtgtgt tccaacagca gacgggrggt gtctactgaa aagggaacct gcttctttac 240
tccagaactc 250

<210> 192
<211> 1902
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (8)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (763)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1898)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1900)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1901)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1902)
<223> n equals a,t,g, or c

<400> 192
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gcaaataaag ckgttattaa cctgaaaaaa aaaaaaanan nn 1902

<210> 193

<211> 560

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (528)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (535)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (559)

<223> n equals a,t,g, or c

<400> 193

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attcccgggt cgaccacgc gtccggggtt gcagacggag gtcagggtctt cctctttcct 120
gagactggat ctgttcaaac agcaaacgcc cacagatggc ccagaggtgg tggtagtcag 180
ggtgtgtggg tgtttttagg gttcttttagt gttgtttctt tcaccagggg gtgggtgtcc 240
cagccagttt ggtgctgacg gtgagaggaa attagaatct gtttgcaaat tgtccaacct 300
acccccctcaa catgaggggc ttccattttc tgtgttttgt aagggaactg tttccttcac 360
gccgccatgt tcctgatatt agttctgatt tctttttaac aaatgttatc atgattaaga 420
aaatttccag cactttaatg gccaatatg tgagaatgta agaaaattga tgctgtacaa 480
ggcaaataaa gctgtttatt aaccttgaaa aaaaaaaaaa aaaggggngg cccgncccat 540

tgccctaggg ggggttaant

560

<210> 194

<211> 590

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (589)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (590)

<223> n equals a,t,g, or c

<400> 194

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tgccggctgc tgaaccggtg tggcgaggcg gcgcggagcc tgcccctggg cgccaggtgt 120
ttcggggtgc ggggtctcgcc gaccggggag aaggtcacgc acactggcca ggtttatgat 180
gataaagact acaggagaat tcggtttgta ggctcgcaga aagaggtgaa tgaaaacttt 240
gccattgatt tgatagcaga gcagcccgtg agcgaggtgg agactcgggt gatagcgtgc 300
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tggcacgcgc ggggtccccgc agcatcctgt gagcatttcc gcggggaagc tgagcacgtg 480
aagctcgctg gttctgtgcg aagggtattc ctggtgctga ataaagggtg ttgctgtcaa 540
gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaann 590

<210> 195

<211> 691

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (10)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (579)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (618)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (639)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (657)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (672)
<223> n equals a,t,g, or c

<400> 195
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ccccaccag tgaatgaatg agaactctgca tttcttgaga tcataagaat actgacatac 120
agatgagata aaactcatgt gaatatcagt ttttaaggctg gtgggttcatt tgttttggtc 180
atattgagtc aggattgact aatgaactgt agagggtttg cattatgcaa atgctcttaa 240
tttcttgat taggaattag acgctcccc ccaagtctta aataatgttt taatctgtat 300
ccttttatta taagaagatt agtaatatc tacagataat aacaacaact ggtatagtat 360
attttattta cattcttcat tcttaggaga aaatgctgag aagcttctgc agttcaagcg 420
ttggttctgg tcaatagtag agaagatgag catgacagaa cgacaagatc ttgkttactt 480
ttggacwtca agcccatcac tgccagccag tgaagaagga ttccagccta tgccctcaat 540
cacaatawga ccaccagatg accmacatct tcctactgna aaatacttgc atttcttgga 600
ctttaccttc ccactctntt cctttaaaca ggattcttna aaccggaaat tggttanctc 660
gccatttagg anccaaaaat tttgggtttt g 691

<210> 196
<211> 1772
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1749)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1769)
<223> n equals a,t,g, or c

<400> 196
gnataatgct ggccattttg ctttctgac atttccttgg gaatctgcaa gaacctcccc 60
tttcccttc cmcaataaga ccatttaagt gtgtgytaaa caactacrga atactaaata 120
aaaagtgttg ccaaaaccaa ccatgaagct gcaaaggtgc ttgctcttac tstttcaaat 180

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ttttgcaact ctartgtctc actttttaaag gaacagcttg attgcaaagg agaaaataga 240
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cagcattcca catcagatct aaagcatcaa atgcctgtga aacagcaaag atgggtgaag 360
attgtgctca ttatgtttgt ggagtgtgta ttgattcaca gtagataacg ctggcagtaa 420
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cagttgcata agcagtgctg tcagaattgg ttggtgcag gcaatagatt ttgccttcaa 540
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stggtagtta cttaagtaat tgaccaaag gaaaagggga agtaattaag gaaattggta 660
agtggaggta gtcaggargt tctygtggy ctyacayag attttacagc ttggstttc 720
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atgttttgta ttgaaactta ataaaacttt aacatggcaa aaaaaaaaaa aaaaaaaaaa 1680
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aaaaaagana aaaaaaaaaa ggggggccnc cc 1772
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<210> 197

<211> 675

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (657)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (671)

<223> n equals a,t,g, or c

<400> 197

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aacatcacgg agctgaatct gccgcagcta gaaatgctca agaaccagct ggaccaggaa 120
gtggagttct tgtccacgct cattgtctag ctcaaagtgg tacagaccaa gtatgtggaa 180
gccaaaggact gtctgaacgt gctgaacaag agcaacgagg ggaaagaatt actcgtccca 240
ctgacgagtt ctatgtatgt ccctgggaag ctgcatgatg tggaacacgt gctcatcgat 300
gtgggaactg ggtactatgt agagaagaca gctgaggatg ccaaggactt cttcaagagg 360
aagatagatt ttctaacc aa gcagatggag aaaatccaac cagctcttca ggagaagcac 420
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gccatgaaac aggccgtcat ggaaatgatg agtcagaaga ttcagcagct cacagccctg 480
ggggcagctc aggctactgc taaggcctga gagtttttgc agaaatgggg cagagggaca 540
ccctttgggc gtggcttcct ggtgatggga agggctctgt gttttaatgc caataaatgt 600
gccagctggg caraaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaccccnggg 660
gggggcccgg nacc 675

<210> 198

<211> 557

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (451)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (461)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (464)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (488)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (492)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (495)

<223> n equals a,t,g, or c

<400> 198

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acgcgtcccg gaacacaaga tgccgaaggg aagaaggcga aggggaagaa ggtggccccc 120
gccccgcgg tcgtgaagaa gcaggaggcc aagaaggtgg tcaacccgct gttcgagaag 180
cggcccaaga acttcggcat cggtcaggac atccagccca agcgggacct gacgcgcttc 240
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aggtgcccgc cgccatcaac cagttcacgc aggcgctgga ccgccagacg gccacgcagc 360
ttgcttgaag ctggcgacaa attaccggcc cgagacgaag caggagaaga agcagcggtt 420
gttgcccccg gcggagaaga aarcggcccg ncaaggggga nttncgaac aagcggsgcc 480
cgttgtntc gnaancgggg ttgaaaacgg ttcaacaagt tggttgagaa acaagaaggc 540

gccattggtt cggtatt

557

<210> 199

<211> 2611

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (3)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2549)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2560)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2585)

<223> n equals a,t,g, or c

<400> 199

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<210> 200

<211> 2316

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2280)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2282)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2302)

<223> n equals a,t,g, or c

<400> 200

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<210> 201

<211> 1147

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (5)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (11)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (12)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1145)
<223> n equals a,t,g, or c

<400> 201
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tggtagcgat cggaggetca gagaacttct acagtgtgtt cgagggcgag ctctccgata 240
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cggnac 1147

<210> 202
<211> 688
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (477)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (684)

<223> n equals a,t,g, or c

<400> 202

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agatatacctc aacgtgaggc tctgctgccca tgaagtgaa gattaagtgc tggaacggcg 240
tggccacttg gctctgggtg gccaacgatg agaactgtgg catctgcagg atggcattta 300
acggatgctg ccctgactgc aagggtgccg gcgacgactg cccgctggtg tggggccagt 360
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cgccctgag ctgcaacaag gtggaaacaa gggctggagc tgcgtttgtt ttgccatcac 600
tatgttgaca cttttatcca ataagtgaat actcattaaa ctactcaaat cttaaaaaaa 660
aaawaaawaa atctcggggg ggncccg 688
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<210> 203

<211> 304

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (269)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (287)

<223> n equals a,t,g, or c

<400> 203

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taactctaga gccattctc ctaaccactg agccatgatt gtcttacaat tttgaatact 120
gcaaaactgg aagaattgtc tggctattat ctaagctgtt cataagctgg aacaagtaga 180
tctgagggtg agaggagttc tgttttaact aggactgagt ttcaaataga gatgtttcag 240
actatagagg gggaaaaatg gcckgggag tccataaatc taagccngtt tcatggatgt 300
tttt 304
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<210> 204

<211> 417

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (380)

<223> n equals a,t,g, or c

<400> 204

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cgaagagcga ggttctgggc gagcgctgaa cgcgggccc aagcaccgcg ggtctttaca 180
cagtcgcggt ccacagactc tgacgaagac gtggatctgc tctcgcttta gctgctcgcg 240
gtcctccaga tcatgtccgc gactcctccq actccgcgcg gaaaaaaaaaag ttgcccaggc 300
gtggactcaa tgacytttcc aastgtgcgc ctcgytgccct ggaccgggtt gagcgcgggt 360
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<210> 205

<211> 551

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (450)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (458)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (471)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (484)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (519)

<223> n equals a,t,g, or c

<400> 205

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gtctgagaca gacatccctg aagcggaggc tctgtcaaat caatactgcg tcgcacttrg 180
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gcggggccac gcagggatgc tgttcccaan tcacgganta tctggtgggc ntcgcaatgg 480
ccantgggac agatggcacg tgaaaggggc cgttccggnt ctcaagcggc agaagcacia 540
gaccgcggag g 551

<210> 206

<211> 1101

<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (21)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (479)
<223> n equals a,t,g, or c

<400> 206
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<210> 207
<211> 515
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (428)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (439)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (449)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (456)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (474)
<223> n equals a,t,g, or c

<400> 207
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ccgctgtatc gcatgcgaat ctttgcacct aatcacgtgg tcgccaagtc ccgcttttg 180
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ccgtcaccca gtggttaccg agacatgggc gcccgacacc gttgcccag cgcattcgat 420
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agcatttcca aggattccaa gatcaattcc cattg 515

<210> 208
<211> 269
<212> DNA
<213> Homo sapiens

<400> 208
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aatctggaca tcattttccc ttccagagca tagaatgcag ggggatccag ggaatggggt 180
aacagaagag gaagctggwt caaggagacc ttgctgtacc aggtgaaggt gtttgaactt 240
tgttcttgca ggcaggcaga gcacggaca 269

<210> 209
<211> 734
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (278)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (732)
<223> n equals a,t,g, or c

<400> 209
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ccgcggacgc ccgctgagct tggcgacacg gccgaccagg agctggtgac tgcctcatg 120
tgtgatttgc ggcggccagc ggcaggtggg atgatggact tggcctacgt ctgtgagtgg 180
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gtcaagtctt caccygttct cacgctgttc ggcggcaagc catggagggc tggatcgcg 660
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caccgagagc tntt 734

<210> 210

<211> 658

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (561)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (567)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (577)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (580)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (636)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (654)

<223> n equals a,t,g, or c

<400> 210

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gtcggtgccg atggcgcaaa ctgatggtg cggcgacatc tctaccgga tcatcaaate 180
cgtaaatatg tcgctatcca gcagtggttc gcggagaaac atccgggtgce gttctactcc 240
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<210> 211

<211> 204

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (91)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (94)

<223> n equals a,t,g, or c

<400> 211

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tatgcttacg acctgcagat acagtctgtt nttncacatg aagaaagtct caagttgctg 120
aagactgaat tgtaagaaaa atctccagcc ctctgtctg cagcttgaga cttgaaccag 180
agagtgtgag agctgctgtt ggag 204

<210> 212

<211> 1271

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1222)

<223> n equals a,t,g, or c

<400> 212

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cgtggaaaaa tacgagaaac agatcaagca ctttggcatg ctctgcgctt gggatgacag 180
ccaaaagtac ctgtcagaca acgtccacct ggtgtgcgag gagacagcca attacctggt 240
catttggtgc attgacctag aggtggagga gaaatgtgca ctcatggagc aggtggccca 300
ccagacaatc gtcatgcaat ttatcctgga gctggccaag agcctaaagg tggacccccg 360
ggcctgcttc cggcagttct tactaagat taagacagcc gatcgccagt acatggaggg 420

cttcaacgac gagctggaag cettcaagga gcgtgtgcgg ggccgtgcca agctgcgcac 480
cgagaaggcc atgaaggagt acgaggagga ggagcgcaag aagcggctcg gccccggcgg 540
cctggacccc gtcgaggtct acgagtcctt ccctgaggaa ctccagaagt gcttcgatgt 600
gaaggacgtg cagatgctgc aggacgccat cagcaagatg gacccacccg acgcaaagta 660
ccacatgcag cgtgcatctg actctggcct ctgggtcccc aactctaagg ccagcgaggc 720
caaggaggga gaggaggcag gtcctgggga ccattactg gaagctgttc ccaagacggg 780
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ctctgttttc actgttcgtc tgcgtctgt gtcttctatt tggcaaacag caatgatctt 1200
ccaataaaag atttcagatg cnaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaacaaaaa 1260
aaaaaaaaa g 1271

<210> 213

<211> 1025

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (991)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1007)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1019)

<223> n equals a,t,g, or c

<400> 213

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ccgga 1025

<210> 214
<211> 351
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c

<400> 214
ggcacgagtr aactatatac ctcaagaat tagaaaaaga agaacaact aagctcaaag 60
ttagcagaag gaaggaaata gtaaatatta cagcagaagt aaagtagagg ctagaaaaat 120
aataaaaaag atcaacaaaa tggattttgt tctcatacta tgataaagac atacttgaga 180
accgcattat ttatggggaa aagaagttaa attgactcac agttccacag gctgtacagg 240
aggcatggct tagggaggcc tcagggaaac ttagratcca tgggtgaagg tgkargagga 300
agcatgcacc atcttctactg gccagagcag gnggagagag agcaaatttg g 351

<210> 215
<211> 1087
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1075)
<223> n equals a,t,g, or c

<400> 215
gctggagtcc cagtccaccc gccacgccc agcagggcct gtccgccttc tacctctcct 60
actttgacat gctgtacct gaggacagca gctgggcagc caaggcccct ggggccagca 120
gtcgggagga gccacctgag gagcctgagc agtgcccgtt cattgacagc caagcccaga 180
cgggcagcct ggacttggtg cccggcgggc tgaccttga ggagcactcg ctggagcagg 240
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cagagcacca ataccggctg ccccccattg gcaaggcctt ccaggagctg gcgggcaagg 420
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caaccaactg cccaggggga tatgggtcct cttggggcct tcgggaccct ggggncaagg 1080
ggcttttc 1087

<210> 216

<211> 1977

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (11)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1873)

<223> n equals a,t,g, or c

<400> 216

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agcgagggca gggagagaag tcagccacgc cctcacggaa gattctggac cctaactctg 180
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<210> 217

<211> 2815

<212> DNA

<213> Homo sapiens

<400> 217

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gcttccaact agttaaatgc ccttgagcgc gggtttccgc ggcccggctc ttgcccccg 180
cggcgcgagt tgagcgttt cccgcgctg tccgcgcggg cgctccgaca gcggtctgc 240
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taacccctc ccacccctct ccatgtccgt gtgtactcgc gctcgggtcca cctggcgcg 480
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<210> 218

<211> 1645

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (347)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1643)

<223> n equals a,t,g, or c

<400> 218

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tgtccggctt tgctggccca gcaagcctga taagcatgaa gctcttatct ttggtggctg 120
tggtcgggtg tttgctggtg ccccagctg aagccaacaa gagttctgaa gatatccggt 180
gcaaatgcat ctgtccacct tatagaaaca tcagtgggca catttacaac cagaatgtat 240
cccagaagga ctgcaactgc ctgcacgtgg tggagcccat gccagtgcct ggccatgacg 300
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aatcaaggaa gccatcatta aattgtttta tttctctcaa aaaaaaaaaa aaaaaaccaa 1560
aaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 1620
aaaaaaaaa aaaaaaaaaa aangg 1645

<210> 219

<211> 478

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (344)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (415)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (452)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (469)

<223> n equals a,t,g, or c

<400> 219

tcgacccacg cgtccgggga attcaaggag acggggggcga cgcgggtgct ggcgcctcct 60
cgggtttggg gctgccgcca tcatgccggg gatagtggag ctgcctactc tggaggatct 120
gaaagtgcag gaggtgaaag tcagttcttc ggtgctcaaa gctgccgccc atcactatgg 180
agttcagtggt gacaagccca acaaggagtt catgctctgc cgtcgggaag aaaaagaccc 240
ccggcggtgt ttagaggaag gcaagctcgt caacaaktgt gctctggayt tcttcaggca 300
gataaagctt tcaactgtgca gagcctttta cagactattg gacntgcac gactactccg 360
gcctgcagtg ttttcgtcgc tgccgcaaac agcaggccaa ttgacgatg tgtgnggggc 420
aactgggatg gtgcggctga actggggaaa angttccagt caccaaatng aaaacagt 478

<210> 220

<211> 832

<212> DNA

<213> Homo sapiens

<400> 220

attttagtag agacaagggtt tcaccatggt ggccaggctg gtctcgaact cctggcctca 60
ggtgatccac ctgccttggc ctcccaaagt gctccgatta caggtgkgag ccacccggcc 120
cagccctcc cttgtgtttc aaccaatcgg aagtgaattt aactagatgt agtaaccttt 180
ttttcttta cttctaaaaa agttacagtt tactaataaa gttaagtctg gttctgtcct 240
agaggaaata aattcactat taattcatgt cttaagttac ttgggttaaa acactttcag 300
ccacccagat taattaaagt ggagcagtggt agccctggc tgggagatgg cctccagagg 360

agcagctgca gggcaygttc tgggcttagc gacagaggca agcaaggagc tgggtgtctct 420
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tcctctgtgg tcaactgact actgcgtatc gcagtggagt aagactgcac agttgctggt 540
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tttataacaa ggattttttt tttagctttg ttaactgtga attcaccctt cctcctccac 660
tgcataattta aagcatgtgt tcacactgtg tgtaaacatt cactgaagat ttttctttt 720
tgcattgctg actgttcaaa cataacaagt attattaaaa ttaaataatta actgacaaaa 780
aaaaaaaaa aaaactcgag gggggggccc gtaccaatt cgcccgaggt ag 832

<210> 221

<211> 1892

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1892)

<223> n equals a,t,g, or c

<400> 221

tgactctggg ctagagacct ccccaacaga gctgaggcca aggccgactc cccctctcaa 60
atggcgtggt ctgggcctat gacggcccct gcagtggagt ctgtactggc tgcgggggac 120
cctgctcatt tgaaaatctg acatcagctg ggcagtcgcc cccctcctcc tttcctccct 180
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gacagtacgc cactcagccc ctgtgcattt ctactacagg accgactgtg attcctccac 780
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1892

<210> 222

<211> 868

<212> DNA

<213> Homo sapiens

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<222> (1)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (23)

<223> n equals a,t,g, or c

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<221> misc feature

<222> (31)

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<222> (45)

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<221> misc feature

<222> (829)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (860)

<223> n equals a,t,g, or c

<400> 222

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<210> 223

<211> 1516

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1493)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1497)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1508)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1509)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1516)

<223> n equals a,t,g, or c

<400> 223

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<210> 224

<211> 1306

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (148)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (887)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1242)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1264)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1303)

<223> n equals a,t,g, or c

<400> 224

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<210> 225

<211> 584

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (486)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (542)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (562)

<223> n equals a,t,g, or c

<400> 225

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gtggcnagaa ggtgacggtg atcaccaagc acaacgatga cgagcattac gcctgggagt 540
cntccgcagg ggctcgttca angttccgca ttgacacagt gaac 584

<210> 226

<211> 523

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature
<222> (34)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (498)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (514)
<223> n equals a,t,g, or c

<400> 226
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gaccatgcc aagcacagtg tgatctcctg gggcccgga tggctgacat gtgcaagaac 180
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<210> 227
<211> 2377
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (2369)
<223> n equals a,t,g, or c

<400> 227
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<210> 228

<211> 463

<212> DNA

<213> Homo sapiens

<400> 228

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aaaactatga acctggacaa aaatcaaggc ccagtatcaa gcacgatata tatagctatg 360
cagttatcac atgggaagtg ktatccagaa aacagccttt tgaagatgtc accaatcctt 420
tgcagataat gtatagtgtg tcacaaggac attggactgg tat 463

<210> 229

<211> 1232

<212> DNA

<213> Homo sapiens

<400> 229

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<210> 230

<211> 1063

<212> DNA

<213> Homo sapiens

<400> 230

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<210> 231

<211> 1063

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1056)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1061)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1063)

<223> n equals a,t,g, or c

<400> 231

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<210> 232

<211> 1474

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1337)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1359)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1377)

<223> n equals a,t,g, or c

<400> 232

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<210> 233

<211> 1782

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (8)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (34)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (591)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1760)

<223> n equals a,t,g,.or c

<400> 233

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<210> 234

<211> 2208

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1314)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2189)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2202)

<223> n equals a,t,g, or c

<400> 234

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<210> 235

<211> 2580

<212> DNA

<213> Homo sapiens

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<221> misc feature
<222> (1)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (3)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (2558)
<223> n equals a,t,g, or c

<400> 235

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<210> 236

<211> 3008

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (3001)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3008)

<223> n equals a,t,g, or c

<400> 236

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<210> 237

<211> 877

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (834)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (854)

<223> n equals a,t,g, or c

<400> 237

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<210> 238

<211> 3039

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (177)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (3039)

<223> n equals a,t,g, or c

<400> 238

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<210> 239

<211> 1992

<212> DNA

<213> Homo sapiens

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<221> misc feature

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<223> n equals a,t,g, or c

<220>

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<221> misc feature

<222> (13)

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<221> misc feature
<222> (29)
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<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1989)
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<400> 239
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aaaaaaaaanc cc 1992

<210> 240

<211> 497
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<213> Homo sapiens

<220>
<221> misc feature
<222> (387)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (476)
<223> n equals a,t,g, or c

<400> 240
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attgaccatt ttggagc 497

<210> 241
<211> 316
<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (133)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (311)
<223> n equals a,t,g, or c

<400> 241
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<210> 242
<211> 829
<212> DNA

<213> Homo sapiens

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<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (3)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (4)
<223> n equals a,t,g, or c

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<221> misc feature
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<223> n equals a,t,g, or c

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<221> misc feature
<222> (47)
<223> n equals a,t,g, or c

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<221> misc feature
<222> (793)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (809)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (814)
<223> n equals a,t,g, or c

<400> 242
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<210> 243

<211> 838

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (32)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (51)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (822)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (832)

<223> n equals a,t,g, or c

<400> 243

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<210> 244

<211> 2853

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2665)

<223> n equals a,t,g, or c

<400> 244

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<210> 245

<211> 1197

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (218)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1193)

<223> n equals a,t,g, or c

<400> 245

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<210> 246

<211> 848

<212> DNA

<213> Homo sapiens

<400> 246

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<210> 247

<211> 1336

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (26)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1336)

<223> n equals a,t,g, or c

<400> 247

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<210> 248
<211> 1076
<212> DNA
<213> Homo sapiens

<400> 248
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<210> 249
<211> 2425
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (52)
<223> n equals a,t,g, or c

<400> 249
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<210> 250

<211> 1408

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (252)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1387)

<223> n equals a,t,g, or c

<400> 250

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<210> 251

<211> 494

<212> DNA

<213> Homo sapiens

<400> 251

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gccagccaag gacagggtg actgcggcta ccccatgtc accccaagg agtgcaacaa 180
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cctttgttcc cggcaagcgc ttctgtgtaa agttcatatc tggagcctga tgtcttaacg 420
aataaaggct ccatgtcca cccgaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 480
aaaaaaaaaa aagg 494

<210> 252

<211> 2491

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (16)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2457)

<223> n equals a,t,g, or c

<400> 252

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<210> 253

<211> 1125

<212> DNA

<213> Homo sapiens

<400> 253

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<210> 254

<211> 1409

<212> DNA

<213> Homo sapiens

<400> 254

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<210> 255
<211> 490
<212> DNA
<213> Homo sapiens

<400> 255
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<210> 256
<211> 1233
<212> DNA
<213> Homo sapiens

<220>
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<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (602)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (931)
<223> n equals a,t,g, or c

<400> 256
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<210> 257

<211> 2404

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (2372)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2385)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2395)

<223> n equals a,t,g, or c

<400> 257

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<210> 258

<211> 2092

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (31)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (60)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2069)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2071)

<223> n equals a,t,g, or c

<400> 258

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<210> 259

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature
<222> (377)
<223> n equals a,t,g, or c

<400> 259
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tatatacata tatatatattc tttaaatttt tgagtctttg atatgtctaa aatcattcct 300
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actgaaaaaa aaaaacnggg ggggccg 387

<210> 260
<211> 3712
<212> DNA
<213> Homo sapiens

<400> 260
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<210> 261

<211> 897

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (22)

<223> n equals a,t,g, or c

<400> 261

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<210> 262

<211> 1905

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1266)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1791)

<223> n equals a,t,g, or c

<400> 262

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<210> 263
<211> 1424
<212> DNA
<213> Homo sapiens

<400> 263
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<210> 264
<211> 1287
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (111)
<223> n equals a,t,g, or c

<220>
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<222> (889)
<223> n equals a,t,g, or c

<220>
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<222> (1196)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1229)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1284)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1287)
<223> n equals a,t,g, or c

<400> 264
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ccgtcccgcg gccccagcc gcccccaacc ctgccccacg ggcccggcgc catgagtggag 180
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tccctgcctt tccaaccaag tttngtn 1287

<210> 265
<211> 991
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature

<222> (421)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (966)

<223> n equals a,t,g, or c

<400> 265

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ggcagactga acggctgcac caggagggca cactggctcc ccctatactg gagctgcggg 240
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aggggacgct cttccgcaag atcagcagcc ggcggcgcca ggataagctg tggttctgct 360
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caaggactgc ccccatgtcc gggagaaggg ctccgggaag cagaacaagg acctctatga 540
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa a                                     991
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<210> 266

<211> 2320

<212> DNA

<213> Homo sapiens

<400> 266

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cggcctgcgc cggcccggc catggcgcc ccccgccgt ctcccgcat ctccgtttcg 180
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cggccgcccc ctccccgat cgaggaatca tttccccctg cgcctctgga ggaggagatc 480
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```

<210> 267

<211> 423

<212> DNA

<213> Homo sapiens

<400> 267

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aattcggcac gaggattgcc ctacccaag tcagtgtgtg gtggcccgaa ccttaggcaa 60
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aggrgagctc tggagggtgg acatccccct gaagctcgtg atgatcgtg gcacgattg 180
tkaccatgac atgacagctg ggcggaggtc aatcgagga ttgttgcca gcatcaatga 240
agggatgacc cgctggttct cacgtgcatt atttcaggat agaggacagg agctggtaga 300
tgggctcaaa gtctgcctgc aagcggctct gagggcttg aatagctgca atgagtacat 360
gcccagccgg atcatcgtgt accgsgtggc gtaggagacg gccagytgaa aacactgggtg 420
act

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423

<210> 268

<211> 1846

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1776)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1816)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1832)

<223> n equals a,t,g, or c

<400> 268

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tcactcagag gaaaaatgaa aaggaacaag aaagaagatt gcagcaggca gtgttaagca 180
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gtgtctttat gcctcgacct caagctgtgg gctcttccaa ttatgcttcc accagtgccg 420
gactgaagta tcctggaaagt ggggctgacc ttctctctcc ccaaagagca gctggagaca 480
gtggtgagga ttcagacgac agtgattatg aaaatttgat tgaccctaca gagccttcta 540
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tagccctgag gtagttcatg aaaatgctgt gcactncatt ccatgggaat gaaatgttgg 1800
aaagctgatc ttttcnggat ataaaatgtt gnatgatgaa aaaaaa 1846
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<210> 269

<211> 601

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (536)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (556)

<223> n equals a,t,g, or c

<400> 269

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gtctcatact ctacaccagt attgctgtcc tactcaggtc cttgactcca tgaagcttac 180
cccctcaggg aggctggcag agagcaggga agaggaggag gaggaggaga ctgaggaaga 240
ggaagaggaa gacgctcacc agttctgctg tccggcctcc gagtgcagta gtccctcttc 300
tcggtaactg agaggacaag ggccattttc tatgcagaag caaaagcctt aaccagsccc 360
tccttcccc caccacccc cccgcagatt ccccatggg accctgtccc ctgcttcagg 420
aaccagatgg gcaagcatcg tgccccctcc tccccccacc ttcttcttgg aattcccatc 480
cccactgctg tctcctctgg actccagccc ctgaattaaa gaaactggag ccctangtcc 540
gactaaaatt tggganaagc aaacttgac ttggacttgg aactggatcc tcccgtaccc 600
g
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601

<210> 270

<211> 880

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (876)

<223> n equals a,t,g, or c

<400> 270

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caagaacac tgattttctt tcaggggagac ttcattgtgt catttatctt caccacagca 720
gattttaaga aattataata tgtaatatgt gatattctata aagagtatat ctaacgtgaa 780
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880

<210> 271

<211> 2484

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (194)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (623)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2396)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (2484)

<223> n equals a,t,g, or c

<400> 271

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tgtaatttc cccgtttttt gggn 2484

<210> 272

<211> 751

<212> DNA

<213> Homo sapiens

<400> 272

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<210> 273

<211> 3309

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (3279)

<223> n equals a,t,g, or c

<400> 273

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<210> 274

<211> 843

<212> DNA

<213> Homo sapiens

<220>
<221> misc feature
<222> (780)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (833)
<223> n equals a,t,g, or c

<400> 274
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<210> 275
<211> 2028
<212> DNA
<213> Homo sapiens

<400> 275
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<210> 276

<211> 1455

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (759)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1408)

<223> n equals a,t,g, or c

<400> 276

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<210> 277

<211> 1923

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1814)

<223> n equals a,t,g, or c

<400> 277

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gga 1923

<210> 278
<211> 1380
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (1293)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1297)
<223> n equals a,t,g, or c

<400> 278
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<210> 279
<211> 1018
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (818)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1017)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1018)

<223> n equals a,t,g, or c

<400> 279

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<210> 280

<211> 1192

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1105)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1130)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1154)

<223> n equals a,t,g, or c

<400> 280

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<210> 281

<211> 1755

<212> DNA

<213> Homo sapiens

<400> 281

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<210> 282

<211> 1093

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (90)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (970)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1081)

<223> n equals a,t,g, or c

<400> 282

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<210> 283

<211> 1556

<212> DNA
<213> Homo sapiens

<220>
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<222> (1324)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1339)
<223> n equals a,t,g, or c

<400> 283
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<210> 284
<211> 1029
<212> DNA
<213> Homo sapiens

<220>
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<222> (828)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (958)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (972)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (976)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (987)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1007)
<223> n equals a,t,g, or c

<400> 284
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cgactactcc gacctggcct tgctcctgca gatccccacg cagaatgcac agggccggca 180
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ccgtgtttt 1029

<210> 285
<211> 1583
<212> DNA
<213> Homo sapiens

<220>

<221> misc feature
<222> (1411)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1531)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (1557)
<223> n equals a,t,g, or c

<400> 285
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gccgagctga ccaacaggac acacagattc ctggagaaaag ccaaggcctt gaagatcagt 180
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gaagccgaaa gcctagacaa cactgtgaaa gaacttgctg aacaactgga atttatcaaa 480
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gggggaggcc gaattttttg gaa 1583

<210> 286
<211> 1177
<212> DNA
<213> Homo sapiens

<400> 286
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aagayatctc aaaatgttta ccaatgtttt aagaagcttt gtgtgatatt cttccaaatg 120

tagttaccaa atataatatg gtagaaaagg ctaaatacata cttaatgagc aaattgaagt 180
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tgaacatttg cctcaagatg ttaactataa acacactgca tacaattttc ttctgaataa 300
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atattttgat aatattttta cagtgaagctt tcccatgttt ttatgtctta agtttctttg 780
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<210> 287

<211> 506

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (394)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (470)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (481)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (494)

<223> n equals a,t,g, or c

<400> 287

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aaacaaagga ctatttataa atacagttaa ttaacaaacg tgaactactt tctgttacat 120
taggtgttcc ctagtgtttc ttaatttctt ttagaaaagt gtatttttat tagtattttt 180
ccggtgaaca gaagatttgt ttggatttaa acatttacta agacagtacc tattaggaaa 240
accaaatatt gcaaatggtc aattcgattt taatttctca aaagatactc tgttatccag 300
aagattaaaa tgcctacatt gagtgtctaa aaaaaaaaaa acmactgtga tratktgagc 360

agaatggcca gtaagttaag ccttttttga tccnggtaat ccagggtatc catttaccat 420
ggaaagggga ttccccaac tactggcca gaggaagtt tggtttttn aaatttaagg 480
nggggaaatt ttanccctat aaaatt 506

<210> 288
<211> 948
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (3)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (926)
<223> n equals a,t,g, or c

<400> 288
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tcggggaaat ccaccgtggg cgccctgctg gcatctgagc tgggatggaa attctatgat 120
gctgatgatt atcaccggga ggaaaatcga aggaagatgg gaaaaggcat accgctcaat 180
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gctgagatgc agctcctggt ggtccatctg agcgggtcgt ttgaggtcat ctctggacgc 420
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gcccatacta gattctaaat gtttctaaag gcaaacccca atgtgtcaag acagacttgt 720
ttaggtgtaa ttttaggaat tatgctggt catcaggaag cagaggggga gttttaaag 780
tcaagcttaa attgaagttt aaattcatct ataaccaaat caaatgatca gaggaaattc 840
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cacaataaaa tgaaacttcg ctgtcnaaaa aaaaaaaaaa aaaaaaaaaa 948

<210> 289
<211> 1034
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (376)
<223> n equals a,t,g, or c

<400> 289
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gccattgggg gccttggaag ccagccatgt cctttgggct ctgtggagag ctttagcctt 180

gcacggcggc gctgggaggc attgcctgcc atgcccactg cccgctgctc ctgctctagt 240
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tctggagttg accaggccta cccagttgc cattcctgaa aaatctcagc tgccaggctg 720
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aaaaaaaaaaaa 1034

<210> 290

<211> 3091

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (24)

<223> n equals a,t,g, or c

<400> 290

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<210> 291

<211> 518

<212> DNA

<213> Homo sapiens

<400> 291

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<210> 292

<211> 498

<212> DNA

<213> Homo sapiens

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<400> 292
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<210> 293
<211> 469
<212> DNA
<213> Homo sapiens

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<210> 294

<211> 668

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (568)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (650)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (652)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (658)

<223> n equals a,t,g, or c

<400> 294

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<210> 295

<211> 1400

<212> DNA

<213> Homo sapiens

<400> 295

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<210> 296

<211> 960

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (599)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (859)

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<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (959)

<223> n equals a,t,g, or c

<400> 296

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<210> 297

<211> 657

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (29)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (86)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<400> 297

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<210> 298

<211> 892

<212> DNA

<213> Homo sapiens

<400> 298

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<210> 299

<211> 1624

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1621)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1623)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1624)

<223> n equals a,t,g, or c

<400> 299

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<210> 300

<211> 1969

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<400> 300

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<211> 1882

<212> DNA

<213> Homo sapiens

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<211> 2804

<212> DNA

<213> Homo sapiens

<400> 302

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<222> (889)

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<221> misc feature

<222> (890)

<223> n equals a,t,g, or c

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<400> 306

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<221> misc feature

<222> (664)

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<212> DNA

<213> Homo sapiens

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<222> (6158)

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<210> 311

<211> 2163

<212> DNA

<213> Homo sapiens

<400> 311

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<210> 312

<211> 1397

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1397)

<223> n equals a,t,g, or c

<400> 312

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<210> 313

<211> 4106

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (344)

<223> n equals a,t,g, or c

<400> 313

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<210> 314

<211> 532

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (497)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (498)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (502)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (524)

<223> n equals a,t,g, or c

<400> 314

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<211> 1938

<212> DNA

<213> Homo sapiens

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<220>

<221> misc feature

<222> (1455)

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<210> 316

<211> 818

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (55)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (814)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (818)

<223> n equals a,t,g, or c

<400> 316

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<210> 317

<211> 837

<212> DNA

<213> Homo sapiens

<400> 317

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gaacgccatc ctctttctgc tgagtgaccg aagtggcatg accacgggtt ccactttgcc 720
ggtggaaggg ggcttctggg cctgctgagc tccctccaca cacctcaagc cccatgccgt 780
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<210> 318

<211> 1448

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (878)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1198)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1395)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1397)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1445)

<223> n equals a,t,g, or c

<400> 318

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gcggctgtga agtgaggggg tctaggggag aaaaggggac ggagagcaga ggaaggggtg 240
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aagataaaca gagggagtag tgagaggctt ttccagtggg gaaaatgcct ctgtgggtca 1380
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aaacntgg 1448
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<210> 319

<211> 1493

<212> DNA

<213> Homo sapiens

<400> 319

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aaaatactcc aaccttttct tggaaagtca taacatctca ctgactgaac attccagtgt 180
gccagtggaa aaaaatatca ctttagaacg accttctgct gtagaactca catgtcagtt 240
cacaacttct ggggatgtga attcagtaaa tgtgacttg aaaaaagggg atgaacaact 300
taagaattac catgtcagtg ccacagaagg catcctgtat acccagtaca agttttccat 360
cattaatagc gaacaactgg gaagctattc ttgtttcttt gaagaggaaa aggaacgaag 420
gggcacattt aatttcggag tccctgaagt tcagagaaaa aacaaacat tgatcactta 480
tgtgggggat tccgttgtct tgggtgtgtaa atgccgacac tgtgtcctt taaattggac 540
ctggtacagt ggtaatagga gtgtacaggt tcctcttgat gttcacatga atgaaaagta 600
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tgcgatcaat ggaacaaacg cgaatgaac aaggcttaag ataatgcagc tttcagaaga 660
cgataaagga tcttattggt gccatgcaat gttccagttg ggcgagagcc aagaaagtgt 720
tgaactgggt gtgataagtt atttggtgcc cctcaaacca tttcttgaa tagttgttga 780
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attaagaaat gaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaggcgccg cgc 1493

<210> 320

<211> 609

<212> DNA

<213> Homo sapiens

<400> 320

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gagcatccag cgagtcctgc aggtctgtga taaagccaat ggatactgtt tcggagccca 180
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tggtgccaag cagaacaccc ccatactgt cagtgggtgc cgtgagctct ggccttgcca 540
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ttattttct 609

<210> 321

<211> 502

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (458)

<223> n equals a,t,g, or c

<400> 321

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tgcccgggcc ccactagc ccagtgtgg gtcagagagg cgtttccatc aaccagtttt 240
gcaaggagtt caatgagagg acaaaggaca tcaagggaagg cattcctctg cctaccaaga 300
ttttagtga gcttgacagg acatttgaat ttaagattgg acagccact gtttctact 360

tcctgaaggc agcagctggg attgaaaagg gggcccggca aacagggaag gaggtggcag 420
gcctggtgac cttgaagcat gtgtatgaga ttgcccgnat caaagctcag gatgagccat 480
ttgcctgcag gatgtacccc tg 502

<210> 322

<211> 2630

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (1952)

<223> n equals a,t,g, or c

<400> 322

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acccttccgg caccctctga cagcccagga tgctgttggc caccctcctc ctccctcctc 180
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tccagccact gatctccctg tgtgaggcac ctcccagccc tctgcagctg cccgggggca 480
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<210> 323

<211> 1874

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (67)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (1735)

<223> n equals a,t,g, or c

<400> 323

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agtggaatcg gtcccgcggt cgagtgggtc tctagtccgg cgccagccgc ccggcccagc 180
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tgccttcaat cagtgttcat atttatagcc aagtgccttc tcatctgtga gacagaatcg 1800
agctargggg cttcagccca gccctgtgga atggggaccg tcttttcctt accctacat 1860
cacctcagcc ctaa 1874

<210> 324

<211> 2325

<212> DNA

<213> Homo sapiens

<400> 324

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acagttttat acattttgag ttgttcataa agtttgtctt gtgatagtc tggcacttaa 180
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tatgtttgac taaagctctc ttcatatgca ggtttataaa tttgttaggt ctgttgtccc 420
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2325

<210> 325

<211> 785

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (6)

<223> n equals a,t,g, or c

<400> 325

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ggagagcccg gagctgctga accctgagcc caggagactg agcccagagt tgaggctact 180
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ttgacttaag atcccacacc tcacaaacct acagcccaga aaccagaagc ccctatagag 720
gccccagtcc caactccagt aaagacactc ttgtccttgg aaaaaaaaaa aaaaaaaaaa 780
aaaaa 785

<210> 326

<211> 244

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (244)

<223> n equals a,t,g, or c

<400> 326

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gcgtccgacg acagaagggt acggctgcga gaagacgaca gaagggtacg gctgcgagaa 120
gacgacagaa gggtagcggt gcgagaagac kacagaaggg tacggctgcg agaagackac 180
agaagggtac ggctgcgaga agacgacaga aggtacgggt gcgagaagac gacagagggt 240
acgn 244

<210> 327

<211> 2454

<212> DNA

<213> Homo sapiens

<400> 327

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tcccacccctc ccgcccgcgg gcagccctag ctccctccac ttggctcccc tggctccgct 180
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<222> (244)

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<220>
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<400> 335
ctccgcaaat tgaacctnc actcaaaggg aaacaaaagc tggagctcca ccgcggtgac 60
ggccgctcta gaactagtgg ggggcccggt acccaattcg ccctatagtg agtcgtatta 120
caattcactg gccgtcggtt tacaacgtcg tgacnnggaa aacntnnaat ncttccggct 180
cgtatgttgt gtggaattgt naggcgataa caattcacac aggnancagc tataaccatg 240
atnnnnccaa gntcgaaatt aacntnact aaaggggaca aaagtngggg ctccacg 297

<210> 336
<211> 386
<212> DNA
<213> Homo sapiens

<220>
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<222> (50)
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<220>
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<222> (128)
<223> n equals a,t,g, or c

<220>
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<222> (185)

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<222> (187)

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<220>

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<222> (200)

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<222> (204)

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<222> (244)

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<220>

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<222> (251)

<223> n equals a,t,g, or c

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<220>

<221> misc feature

<222> (265)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (272)

<223> n equals a,t,g, or c

<220>

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<222> (275)

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<222> (315)
<223> n equals a,t,g, or c

<220>
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<222> (322)
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<220>
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<222> (328)
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<220>
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<220>
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<220>
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<220>

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<222> (363)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (365)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (380)

<223> n equals a,t,g, or c

<400> 336

gatgggcagc gactacatcc gtgaggtgaa tgtggtgaag tctgcccgtg tcggttattc 60
caaaatgctg ctgggtgttt atgcctactt tatagagcat aagcagcgca acacccttat 120
ctggttgncg acggatggtg atgcccngga actttatgaa aaaccacgt tgagcccgac 180
tattngngat attccgtcgn tgcntggggc tggcccctg gtatggcāaa aaagcaccgg 240
gttnaacaag ntcaaccatg naagngttcc anctnaatgg gggggncccc gtaacccaat 300
tngncctata agtnnatggg antttaanaa ttcaatnggc cctngntttt aaatggtgng 360
tgntnggcct ttttttttn gtttgt 386

<210> 337

<211> 506

<212> DNA

<213> Homo sapiens

<220>

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<220>

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<222> (340)

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<220>
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<222> (412)
<223> n equals a,t,g, or c

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<222> (437)
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<220>
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<222> (439)
<223> n equals a,t,g, or c

<220>
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<222> (469)
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<223> n equals a,t,g, or c

<220>
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<222> (471)
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<220>
<221> misc feature
<222> (472)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (481)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (483)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (501)

<223> n equals a,t,g, or c

<400> 337

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aattcggcag agnattgaca tcaggaagga cctctatgct aacaatgtcc tatcaggggg 60
caccactatg taccttgcca ttgccgaccg aatgcagaag gagatcacgg ccctagcacc 120
cagcaccatg aagatcaaga tcattgcccc tccggaggcg caaatactct gtctggatcg 180
gtgggtccat cctggcctct ctgtccacct tccagcagat gtggatcagc aaacagggaa 240
tacgggtgaag ccgggccttc cattgtccac cgcaaatgct ttcttaaaac acttttcctg 300
gttcctnttc tgtcttttag gcacacaact gtggaatgtn cctgtgggaa tttatggccn 360
tttcagtttc tttttccaaa tcattcctag ggccaaagtt ttgnattggt tnanccatgg 420
ggttttttta aataaantnt ggaaataggg ttaattggtt aaaaaaann nnaaaaaaaa 480
ntntgggggg ggggggcccg ntaccc 506
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<210> 338

<211> 623

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (441)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (508)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (509)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (513)

<223> n equals a,t,g, or c

<220>

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<222> (537)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (565)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (597)

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<220>

<221> misc feature

<222> (599)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (612)

<223> n equals a,t,g, or c

<400> 338

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aagaaggagc tgtctgacat cgctcaccgc atcgtggcac ctggcaaggc catcctggct 120
gcagatgagt ccaactgggag cattgccaag cggctgcagt ccattggcac cgagaacacc 180
gaggagaacc ggcgcttcta ccgccagctg ctgctgacag ctgacgaccg cgtgaacccc 240
tgcattgggg gtgtcatcct cttccatgag acaactctacc agaaggcgga tgatgggcgt 300
cccttcccc aagtatcaa atccaagggc ggtgtgtgtg gcatcaaggt agacaagggc 360
gtgggtcccc tggcagggac aaatggcgag actaccaccc aagggttggg tgggctgtct 420
gagcgctgtg ccagtagaa ngaaggacgg agctgacttc ggccaagtgg cggtgtgtgc 480
ttaagaatgg gggaacacac cccctcannn ctnggcacatc tggaaaatgc caattgntct 540
ggccccgtat gccagtatct ggcancagaa tgcattgggc cattcgggga gtctgananc 600
tcctgatggg ancatgactt gaa                                     623
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<210> 339

<211> 344

<212> DNA

<213> Homo sapiens

<220>

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<222> (88)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (157)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (171)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (210)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (298)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (330)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (343)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (344)
<223> n equals a,t,g, or c

<400> 339
tcgacccacg cgtccgcttc aacatgatit gtcacaatct tatcaataat cattactctg 60
ttttttatat ttcaactaaa agtatcanaa tatagctttc cagaaaaccc cgaaccaaag 120
tacttgacta catcaaagtc tactacacct tggaganaac aaatgaacga naatctatit 180
tcctcattca ttaccccaac aataataggn ctccctatcg taattattat cactatgitt 240
ccaagcatta tattcccatc acctaccgga ctaatcaata atcgactcat ctccattnca 300
acaatggatt agtgcantga acatgcaaan gcaaggatta tcnn 344

<210> 340
<211> 345
<212> DNA
<213> Homo sapiens

<220>
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<222> (6)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (13)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (31)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (88)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (90)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (128)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (135)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (138)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (146)
<223> n equals a,t,g, or c

<220>
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<222> (153)
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<222> (172)
<223> n equals a,t,g, or c

<220>
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<222> (173)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (296)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (313)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (339)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (343)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (345)
<223> n equals a,t,g, or c

<400> 340
agacangctc tantacgact cactataggg naaagctggt acgcctgcag gtaccggtcc 60
ggaattcccc ggtcgacca cgcgtccngn aggaggggac agctgcgggc gcggggaggg 120
ggcgccgngc cgcgnggngc catgngggac agnagagccg ggagtccgag annccgggcc 180
gcagcccag atgtcgccgc catggcttcg ccgcagctct gccgcgcgct ggtgtcggcg 240
caatgggtgg cggaagcgct gcgggccccg cgcgctgggg cagcctctgc agctgntagg 300
acgcctcctg gtnacctggc cggaagctgg ggggcgcgna cgnen 345

<210> 341
<211> 170
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (20)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (43)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (86)

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<222> (160)

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<220>

<221> misc feature

<222> (163)

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<220>

<221> misc feature

<222> (164)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (170)

<223> n equals a,t,g, or c

<400> 341

acccacgcgt ccgcccacgn tcncgactag ttctagatcg cgnacggccg ctctagagga 60
tccaagctta cttggacatg catgcnacgt catagctctt ctatagtgtc acctaaattc 120
aattcactgg ccgtcgtttt acaacgtcgt gactgggaan atnntaaan 170

<210> 342

<211> 387

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (238)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (273)

<223> n equals a,t,g, or c

<220>
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<222> (328)
<223> n equals a,t,g, or c

<220>
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<222> (337)
<223> n equals a,t,g, or c

<220>
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<222> (351)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (366)
<223> n equals a,t,g, or c

<220>
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<222> (384)
<223> n equals a,t,g, or c

<400> 342
aatgacttgg ttgagtactc accagtcaca gaaaagcadc ttacggatgg catgacagta 60
agagaattat gcagtgtctgc cataaccatg agtgataaca ctgcggccaa cttacttctg 120
acaacgatcg gaggaccgaa ggagctaacc gcttttttgc acaacatggg ggatcatgta 180
actcgcccttg atcgttggga accggagctg aatgaagcca taccaaacga cgagcgtnac 240
accacgatgc ctgtagcaat ggcaacaacg ttngcaaact attaaactggc ggactactta 300
ctctagcttc ccggaacaa tttatagnct tgggtgnggc gggtaaagtt ncaaggccca 360
tttttngggt tggccttccg gttngtt 387

<210> 343
<211> 186
<212> DNA
<213> Homo sapiens

<220>
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<222> (26)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (64)
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<220>

<221> misc feature
<222> (71)
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<220>
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<222> (109)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (152)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (153)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (160)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (183)
<223> n equals a,t,g, or c

<400> 343
gctgcaggaa attaacagag tctacnagga aatgtacaag actgatctgg agaaagacat 60
tatntcggac ncatctggtg acttccgcaa gctgatgggt gccctggcna aagggttaaaa 120
aacagaagaa tggtcogtcc ttgaatatga anngaatan ccacatgcc ggatttcctt 180
ganccc 186

<210> 344
<211> 611
<212> DNA
<213> Homo sapiens

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<222> (8)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (11)
<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<400> 344

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tgcaaggnga nactaccctc actaaaggga acaaaagctg gagctccacc gcggtgcggc 60
cgctctagaa ctagtggatc ccccgggctg caggaattcg gcacgagctg cgttgggctc 120
cgggaaagccg ttcgggctgg ggctgtcggc cgcggggcgg aggcactcgc gcgggggatg 180
gcccactgcg tgaccttggg tcagctgtcc atttctgtg accatctcat tgacaaggac 240
atcggtccca agtctgaccc actctgcgtc cttttacagg atgtnggagg gggcagctgg 300
gctgagcttg gccggactga acgggtgcgg aactgctcaa gccctgagtt ctccaagact 360
ctacagcttg agtaccgctt tgagacagtc cagaagctac gctttggaat ctatgacata 420
gacaacaaga cgccagagct gagggatgat gacttcctag ggggtgctga gtgttccta 480
ggacagattg tgtccagcca ggtactgact ctccccttga tgctgaagct ggaaaacctg 540
ctgggcgggg gaccatcacg gtctcagctc aggaattaaa ggacaatcgt gtagtaacca 600
tggaggtaga g                                     611
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<210> 345

<211> 344

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (296)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (329)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (342)

<223> n equals a,t,g, or c

<400> 345

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tttcttcta cagtattcct gaatttgacg aatggaaaaa acatatagaa aaccagaaag 60
cctggaaaat aaagtactat aaaggattgg gtactagtac agctaaagaa gcaaaggaa 120
attttgctga tatggaaagg catcgcatct tgtttagata tgctggctct gaagatgatg 180
```

```

ctgccattac cttggcattt agtaagaaga agattgatga cagaaaagaa tggtaacaa 240
atattatgga agaccggaga cagcgtagct acatggctta ccagaggant gattcnctct 300
caactcagac atgaaagatc tataccacnc ntgttgatgg cntt 344

```

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<210> 346
<211> 506
<212> DNA
<213> Homo sapiens

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<220>
<221> misc feature
<222> (392)
<223> n equals a,t,g, or c

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```

<220>
<221> misc feature
<222> (452)
<223> n equals a,t,g, or c

```

```

<220>
<221> misc feature
<222> (453)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (472)
<223> n equals a,t,g, or c

```

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<220>
<221> misc feature
<222> (480)
<223> n equals a,t,g, or c

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<220>
<221> misc feature
<222> (495)
<223> n equals a,t,g, or c

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<400> 346
ggaaaaagccc aaggaaaaag caaagaatag caaaaaaaag ggggccaaga aggaagtgggt 60
tgggattgggt cttctttttt cttcagtgag ttttttcccc aacaggttct gatggtcctt 120
tggctaccag caaaccagtc cctgcagaaa agtcagggtct tccagtgggt cctgagaacg 180
gagtagaact ttccaaagag gagctgatcc gcaggaagcg cgaggagttc attcagaagc 240
atgggagggg tatggagaag tccaacaagt ccacgaagtc agatgctcca aaggagaagg 300
gcaaaaaagc accccgggtg tgggaactgg gtggctgtgc taacaaagaa atgttgatt 360
acagtacttc caccaccaat ggaaccctg angcttgctt tgtctgagga cattaacctt 420
gattccaagg gactgggtct ggggggcact tnnngatctg gactgcacac tntgatgacn 480
aagggttgt taaantttcc aaacta 506

```

```

<210> 347

```

<211> 444
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (289)
<223> n equals a,t,g, or c

<400> 347
cggaagggag accatgttcc gagcgggcggc tccggggcag ctccggcggg cggcctcatt 60
gctacgattt cagagtaccc tggtaatagc tgagcatgca aatgattccc tagcacccat 120
tactttaaat accattactg cagccacacg ccttgagggt gaagtgtcct gcttagtagc 180
tggaaccaa tgtgacaagg tggcacaaga tctctgtaaa gtagcaggca tagcaaaagt 240
tctggtggct cagcatgatg tgtacaaagg cctacttcca gaggaactna caccattgat 300
tttggaact cagaagcagt tcaattacac acacatctgt gctggagcat ctgccttcgg 360
aaagaacctt ttgccagag tagcagccaa acttgagggt gccccgattt ctgacatcat 420
tgcaatcaag tcacctgaca catt 444

<210> 348
<211> 358
<212> DNA
<213> Homo sapiens

<220>
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<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (52)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (187)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (280)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (295)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (301)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (348)
<223> n equals a,t,g, or c

<400> 348
ggcagagaag cagaagcgnc tcagttagag tccagcaaaa ggtttgccaa anagtttatg 60
gacagacatg gaatcccaac cgcacaatgg gaaggctttc accaaacctg aaaggaagcc 120
tgcagcttca ttttgagtgc agacttcctt gctttgggtg tgaaaggcca gtggtcttgc 180
agctggnaaa aggggtgatt gttgcaaaga gcaaagaaga ggcctgcaag ctgtacaaga 240
gatcatgcag gtaggctggg tcttctggaa aaatttactn ttgtattcat actgnatgaa 300
ntaccgtttt aagtttnaaa aatgttcctc acattaaggg aaattctntt ttgcaacc 358

<210> 349
<211> 321
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (187)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (206)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (240)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (294)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (295)
<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (301)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (316)

<223> n equals a,t,g, or c

<400> 349

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tgcggaaccc ctacacgggt gccaccttc tgctggccgc cctgcccacc agcctgctcc 120
tgctgcagtg gtatgagccg ctgcagaagt ttctgctgct gaagaacttc tccagccctc 180
tgcccanccc agctgggatg ctgganccgc tgggtgctgga tgggaaggag ctgccgcagn 240
gtttttttgg ggccgaaggg cctaaagggc ccggttgccg gttcctgttc caannctgc 300
ncctgggagg ttggcnttaa g 321
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<210> 350

<211> 742

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (618)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (653)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (658)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (683)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (689)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (702)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (707)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (714)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (719)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (722)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (734)

<223> n equals a,t,g, or c

<400> 350

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ggtcacgctg acccagtgcg cggaagagct ggtgcagctc atcctgcacg aatacaagat 60
cttcaatgca gaagtgcctt tccgagaaga ctgctccccg gacgagttca tcgatgtgat 120
cgtgggcaac cgggtgtaca tgccctgcct gtatgtttat aacaaaatcg accagatctc 180
catggaagag gtggaccgcc tggcccgaaa acccaacagt gtgggtcatca gctgcggcat 240
gaagctgaac ctggactatc tgctggagat gctctgggag tacttgcccc tgacctgcat 300
ctacaccaag aagagaggac agaggccaga cttcacagac gccatcattc tccggaaagg 360
ggcctcagtg gagcacgtgg gcaccagcac caagtacagt ccgcagcggg tgggcctgac 420
ccacaccatg gagcatgagg acgtcatcca gatcgtgaag aagtaacggc gcctgccggg 480
ccttccgccc acctgctcgt ctcccttggg aggtgggtccc actgggacac acaaacaccc 540
aaacagaaaa atacaaatac acgtacccca agaaggggtc cctcaagtct ctgctattta 600
cagaagtttc ttcagtangc agacaaaaaa tgtgttgggc aaaagggctc ggntggangc 660
attttccata agactgagcc ctnttcatng ggggttttga gnttgantgc ttancctgna 720
tntgtgcctc caanccctg ac 742
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<210> 351

<211> 272

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (167)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (251)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (272)
<223> n equals a,t,g, or c

<400> 351
aatcaggcgg gactgacggc agatcgatg ctggctcgt ccagagccgg gcaggcggca 60
gggtgacgt ttaaccagac cagcgagtca ctcagcgac tggtaaggc gggggtaagc 120
ggtagggctc agattgcgtc catcagccag agtgtggcg gttctnctc tgcacccggc 180
gtggagggtg acaaggctgt tgaagccttc gaggggggcc cgtacccatt tgcctatagt 240
aagcgtatta naataattgc cgtgttttaa an 272

<210> 352
<211> 256
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (170)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (248)
<223> n equals a,t,g, or c

<220>
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<222> (251)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (252)
<223> n equals a,t,g, or c

<400> 352
gcagacgtcc agagcagagt cagccagcat gaccgagcgc cgcgtccct tctcgtcct 60
gcggggcccc agctgggacc ccttcgcga ctggtaccgc catagccgcc tcttcgacca 120

ggccttcggg ctgccccggc tgccggagga gtggtcgag tggtaggcn gcagcagctg 180
gccaggctac gtgcgcccc tgcccccg cgcacgcaga gccccgcagt ggccgngccc 240
gctacagncg nncgct 256

<210> 353
<211> 592
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (35)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (54)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (93)
<223> n equals a,t,g, or c

<220>
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<222> (277)
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<220>
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<222> (480)
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<220>
<221> misc feature
<222> (485)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (522)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (545)
<223> n equals a,t,g, or c

<400> 353
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gctcactcgt tgggtccgtg ccacctttaa aactgtaac actcaccgag aaggtctgca 120
acttcactcc tggggccagc aagaccacga gtgcaccgag aggaatgaac aactctggac 180
acaccatctt taagaaccgt aatactcacc gcaaggggtct gcaacttcat tcttgaagtc 240
agtgaaggcca agaaccatc aattccgtac acatttnggt gactttgaag agactgtcac 300
ctatcaccaa gtggtgagac tattgccaag cagtgaagact attgccaagt ggtgagacca 360
tcaccaagcg gtgagactat cacctatcgc caagtgggtcc taagtgtgaa cgtgaagtcc 420
ccagccctgc tgctgagcca gttgctgccc tacatggaga acaagaaggg tgctgtcatn 480
ctggncctct ccattgcagc ttataatcca gtagtggcgc tnggtgtcta caatgtcagc 540
aaganagagc tgctgggggc tcactagaac actggcattg ggcttggccc cc 592

<210> 354

<211> 539

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (223)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (225)

<223> n equals a,t,g, or c

<400> 354

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aactagtgga tccccgggc tgcaggaatt cggcacgagt cgtctcaggc tcgtagttcg 120
ccttcaacat gccggaacca gcgaagtccg ctcccgcgcc caagaagggc tcgaagaaag 180
ccgtgactaa ggcgcagaag aaggacggca agaagcgcaa ggnanccgca aggagagcta 240
ctccgtatac gtgtacaagg tgctgaagca ggtccacccc gacaccggca tctcctctaa 300
ggccatggga atcatgaact ctttcgtcaa cgacatcttc gaacgcacgc cgggtgaggc 360
ttcccgcctg gcgcattaca acaagcgtc gaccatcacc tccagggaga tccagacggc 420
cgtgcgcctg ctgctgcccg gggagtggc caagcacgcc gtgtccgagg gcaccaaggc 480
cgtcaccaag tacaccagcg ctaagtaaac ttgccaagga gggactttct ctggaatth 539

<210> 355

<211> 435

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (296)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (299)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (396)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (419)
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<222> (421)
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<220>
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<222> (422)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (424)
<223> n equals a,t,g, or c

<400> 355
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atgaggacac actctctgtg gcaactgcat atttctggga gcactttgat aaggacggct 120
ggtcctctgtg gtactcagag tatcgcttcc ctgaagaact cactcagacc ttcagtagct 180
gcaatctcat cactggaatg ttccagcgac tggacaagct gaggaagaat gccttcgcca 240
gtgtcatcct ttttgaacc aacaatagca gctccatttc tggagtctgg gtcttncng 300
gccaggagct tgcctttccg ctgagtcagc attggcaagt ggactacgaa gtcatacaca 360
tggcggaaac tggatctggc aagcgaggag acccanacgc tggttcgaga gtacttttnc 420
nngngagggg gcctt 435

<210> 356
<211> 502
<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (239)
<223> n equals a,t,g, or c

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<222> (243)
<223> n equals a,t,g, or c

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<221> misc feature
<222> (252)
<223> n equals a,t,g, or c

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<222> (275)
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<222> (288)
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<222> (292)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (298)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (316)
<223> n equals a,t,g, or c

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<221> misc feature
<222> (317)
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<220>
<221> misc feature

<222> (324)
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<222> (328)
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<222> (339)
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<222> (364)
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<222> (372)
<223> n equals a,t,g, or c

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<222> (386)
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<222> (390)
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<222> (393)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (397)
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<222> (440)

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<220>
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<222> (457)
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<220>
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<222> (458)
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<220>
<221> misc feature
<222> (459)
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<220>
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<222> (461)
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<222> (476)
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<220>
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<222> (478)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (485)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (497)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (499)
<223> n equals a,t,g, or c

<400> 356
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gaagaatgaa cagaagggag agaagattcc tcggtgcttg ccagtttgtg ggaagcccg 120
gaaccccggt gaacagaggc agcgcacat cggagggcaa aaagccangg ggatagtggg 180
ggcggttttg cagtaaggga cccgaacact gatcgctggg tggccacggg catcggtgnc 240
ctngggcatc gngtgcagca gggccttatg gcttnttaca ccaaagtnc cnaacttncg 300
tggccttgga tcaagnnaga cctngganca ggaggactnc cgccccanca ttcactaggt 360
tccnaatcca gngagcagtt tcgcanaaan canccanaca cancttcccc ctntttngnn 420
accnncagn gtctctnttn anatncctnc tngcacnna ncccacaacc ccccnncnc 480
ccccncccc ccccnncnc cc 502

<210> 357
<211> 440
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (45)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (236)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (262)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (293)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (300)
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<220>
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<222> (316)
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<220>
<221> misc feature
<222> (339)
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<220>
<221> misc feature
<222> (360)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (362)
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<220>
<221> misc feature
<222> (378)
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<220>
<221> misc feature
<222> (387)
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<220>
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<220>
<221> misc feature
<222> (407)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (418)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (426)
<223> n equals a,t,g, or c

<400> 357
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ctgttcaggc cggagccaca gaccgccgtt gaatgggcgg atgctaatta ctatctccc 120
aaagaatccg cataccagga agggcgctgg gaaacactgc cctttcagcg ggccatcatg 180
aatgcgaatg ggcagcgact acatccgtga gtggaatgtg gtgaagtttg cccgtntcgg 240
ttattccaaa atgctgctgg gngtttatgc ctactttata gggcataagc agnggaacan 300
ccttatttgg ttccncagg atgttgatg cccgagaant ttttggaanaa cccacgttgn 360
gncgattatt tcgggganatt ttccgngnt gttggggtt gncccntgg gttttgnaa 420
aaaganccgg gtaaaaggtt 440

<210> 358
<211> 234
<212> DNA
<213> Homo sapiens

<220>
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<222> (16)
<223> n equals a,t,g, or c

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<222> (92)
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<220>
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<222> (166)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (175)
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<220>
<221> misc feature

<222> (208)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (230)
<223> n equals a,t,g, or c

<400> 358
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tgtgatgaag gagatgggag gccatcacat tntagtcctc tttttgctca aggggggcta 120
taaatttttt gctgacctgc tggattacat caaaggactg antagnaaat agtgnataga 180
tccattcctc atgaactgtg gatttttngc agatctgaag agctattgtn atga 234

<210> 359
<211> 668
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (15)
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<220>
<221> misc feature
<222> (19)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (20)
<223> n equals a,t,g, or c

<220>
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<222> (295)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (512)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (552)
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<220>
<221> misc feature

<222> (558)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (559)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (579)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (588)
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<220>
<221> misc feature
<222> (593)
<223> n equals a,t,g, or c

<220>
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<222> (659)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (667)
<223> n equals a,t,g, or c

<400> 359
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aagctggtac gcctgcaggt accggtccgg aattcccggg tcgacccacg cgtccgggggt 120
gtttgaggta cataagaaaa atgtaagggg tgaattcact tattatgaaa tacaagataa 180
tacagggaag atggaagtgg tgggtcatgg acgactgacc acaatcaact gtgaggaagg 240
agataaaactg aaactcacct gctttgaatt ggcaccgaaa agtgggaata ccgngaggtt 300
gagatctgta attcatagtc acatcaaggt catcaagacc aggaaaaaca agaaagacat 360
actcaatcct gattcaagta tggaaacttc accagacttt ttcttctaaa atctggatgt 420
cattgacgat aatgtttatg gagataaggt ctaagtgcct aaaaaaatgt acatatacct 480
ggttgaaata caacactata catacacacc ancatatata ctgcttggtt aatcctatgg 540
aaatggggta tntggagnnc ttttttaatt ttcatagnt tttttttnat aanaatggca 600
tattttggat ctacaacttc tatgatttga aaaaatacct taacccttat cttttttgng 660
aaaaaana 668

<210> 360
<211> 401
<212> DNA
<213> Homo sapiens

<400> 360

caccattacc agcggcggca atcctccggc cttttccctg acaccggacg gaaagctgac 60
cgctaaaaat ggggatatca gtggcagtgt gaatgcgaac tccgggacgc tcagtaaatgt 120
gacgatagct gaaaactgta cgataaacgg tacgctgagg gcggaaaaaa tcgtcgggga 180
cattgtaaag gcggcgagcg cggcttttcc gcgccagggtg gaaagcagtg tggactggcc 240
gtcaggtacc cgtactgtca ccgtgaccga tgaccatcct tttgatcgcc agatagtggg 300
gcttcgctg acgtttcgcg gaagtaagcg tactgtcagc ggcaggacaa cgtattcgat 360
gtgttatctg aaagtactga tgaacgggtc ggtgatttat g 401

<210> 361

<211> 273

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (156)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (189)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (236)

<223> n equals a,t,g, or c

<400> 361

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tgagccgtaa ttatcatctg cgcgggcgta ttctgcagggt gccgtcgaac tataaccgcg 120
agacgcggca atacagcggg atctgggacg gaacgnntaa accggcatac agcaacaaca 180
tggcctggng tctgtgggat atgctgaccc atccgcgcta cggcatgggg aaacgncttg 240
gtgcggcgga tgtggataaa tgggcgctgt atg 273

<210> 362

<211> 248

<212> DNA

<213> Homo sapiens

<220>

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<222> (5)

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<220>

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<222> (37)

<223> n equals a,t,g, or c

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<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (210)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (218)
<223> n equals a,t,g, or c

<400> 362

cgctngtcgg gcgagcgatg atgcggaagg ttacctngat nttttcaaag gnaagataac 60
cgaatcccat ctngcaagg agctgctgga aaaagtcgag ctgacggagg ataacgccag 120
cagactggag gagttttcga aagantggaa ggatgccagt nataagtga atgcatgtg 180
ggctntcaaa attnagcaga ccaaagacgn caaacgantt ttattctgct atttagtagt 240

aagatcag

248

<210> 363

<211> 149

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (131)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (137)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (144)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (145)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (147)

<223> n equals a,t,g, or c

<400> 363

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atctggaggc gacggggctg tatcaggtgc cgttgtcagc ggcacagccg ggcgatgtgc 120
tgctgtgctg ntttgntca tcannngcg 149

<210> 364

<211> 352

<212> DNA

<213> Homo sapiens

<220>

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<222> (4)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (93)

<223> n equals a,t,g, or c

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<222> (196)
<223> n equals a,t,g, or c

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<222> (319)
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<222> (322)
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<222> (325)
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<222> (338)
<223> n equals a,t,g, or c

<220>
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<222> (340)
<223> n equals a,t,g, or c

<400> 364
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tgctctggtt ctcatgacgg cagatgcagc gangaggctc aatgttacac cactggcaag 120
aatagtagca ttgctgacg ctgctgtaga acctattgat tttccaattg ctcctgtata 180
tgctgcattc atggtnctta aagatgtggg attgaaaaaa gaagatattg caatgtggga 240
agtaaatgga agcctttagt ctggttgtag tagcaaacat taaaaatgtt ggagattgga 300
tccccaaaaa gtgaatatnc anggnaggag ctgtttcncn ggggacatcc ca 352

<210> 365
<211> 272
<212> DNA
<213> Homo sapiens

<220>
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<220>
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<222> (42)
<223> n equals a,t,g, or c

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<222> (44)
<223> n equals a,t,g, or c

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<220>
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<222> (91)
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<222> (260)

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<221> misc feature

<222> (261)

<223> n equals a,t,g, or c

<400> 365

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ggcttgtgcc gctgctggan tgacagcctt ncgaggcttt gctgtctcgg cacggnaggt 120
ctggcaaacc anggacagac caggnacatg ggaccaaagc cggaacctcc tgctcaacgg 180
gaagtcctan ccaccaaag tgcgcctgat ctgggggggc tccctncccc cagtcaagcg 240
gncggcggat gaactggatn nacgccccgg at 272
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<210> 366

<211> 254

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (23)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (192)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (208)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (209)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (236)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (244)

<223> n equals a,t,g, or c

<400> 366

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ggctctacta ggactcacta tanggaaagc tggtagcct gcaggtaccg gtccggaatt 60
cccggtcgga cccacgcgtc cgcttctctg cctagaaggg ataattattat cactcttcgt 120
tataataaca atcaccatct taattaacca ccttacatta gccagcataa cccctatcat 180
ccttcttgta tntgcagcct gtgaagcnnn actggggcct atccctttta gttatnatct 240
caantacata cgga                                     254
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<210> 367

<211> 185

<212> DNA

<213> Homo sapiens

<400> 367

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gattggattc gacaacaaaa aagacctgct tatctcgggtg ggcgatttgg ttgatcgtgg 60
tgcagagaac gttgaatgcc tggaattaat cacattcccc tgggttcagag ctgtacgtgg 120
aaaccatgag caaatgatga ttgatggcct atcagagcgt ggaaacgtta atcactggct 180
gctta                                             185
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<210> 368

<211> 458

<212> DNA

<213> Homo sapiens

<220>

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<220>

<221> misc feature

<222> (4)

<223> n equals a,t,g, or c

<220>

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<222> (6)

<223> n equals a,t,g, or c

<220>

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<222> (15)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (27)

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<222> (170)
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<220>
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<220>
<221> misc feature
<222> (340)
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<220>
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<222> (395)
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<220>
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<222> (399)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (404)
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<220>

<221> misc feature
<222> (415)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (433)
<223> n equals a,t,g, or c

<400> 368
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ccggagttag ccttgaacgc ctggacctgg acctcacagc tgacagccag ccacccgtct 120
tcaaggtctt cccaggcagt accactgagg actacaacct tattgttatn gaacgtggcg 180
ctgccgctgc acnaccggcc agccagggac tgcgcctgca ggaacccctg gngccccacc 240
cctggntggn atggccattg tcaaggagga ggagacggag gctgccattg gagccccctcc 300
tactgccact gagggncctg agaccaaacc tgtgcttatn gctcttgagg agggctcctgg 360
tgctgagggg tcccggctgg actcactagt ggcanaacna ctcnnggctgg aagtngtagc 420
tctgagggac tcngccccag tgttggccgg gacctgat 458

<210> 369
<211> 288
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (15)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (17)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (47)
<223> n equals a,t,g, or c

<220>
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<222> (56)
<223> n equals a,t,g, or c

<220>
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<222> (71)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (103)
<223> n equals a,t,g, or c

<220>
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<222> (114)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (225)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (239)
<223> n equals a,t,g, or c

<400> 369
gcgctggagc tgctngngca ctgcggcgtg tgcagagagc gcctgcnacc cgaganggag 60
ccccgcctgc ngccctgttt gcaactcgcc tgtagtgcc gcntagggcc cgcngccccg 120
ccgccgccaa cagctcgggg gacggcgggg cggcggggcga cggcaccgtg gtggactgtc 180
ccgtgtgcaa gcaacagtgc ttctccaaag acatcgtgga gaatnatttc atgcgtgana 240
gtggcagcaa ggctgccacc gacgccagg atgcgaacca gtgctgca 288

<210> 370
<211> 292
<212> DNA
<213> Homo sapiens

<220>
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<222> (47)
<223> n equals a,t,g, or c

<220>
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<222> (53)
<223> n equals a,t,g, or c

<220>
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<222> (60)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (61)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (101)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (141)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (263)
<223> n equals a,t,g, or c

<400> 370
ccatctttgc attgttcctc atccgcctcc ttgctcgccg cagccgntc cgcgcgcgn 60
ntcctccgcc gccgcggact ccggcagctt tategccaga ntccctgaac tctcgcttc 120
tttttaatcc cctgcatcgg ntcaccggcg tgccccacca tgtcagacgc agccgtagac 180
accagctccg aaatcaccac caaggactta aaggagaaga aggaagt ttt ggaaagaggc 240
agaaaatgga agagacggcc ctncctaacg gggaatgcta atttagggaa at 292

<210> 371
<211> 477
<212> DNA
<213> Homo sapiens

<220>
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<222> (35)
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<220>
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<222> (276)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (313)
<223> n equals a,t,g, or c

<220>
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<222> (342)
<223> n equals a,t,g, or c

<220>
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<222> (374)
<223> n equals a,t,g, or c

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<222> (399)
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<222> (410)
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<220>
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<222> (427)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (434)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (447)
<223> n equals a,t,g, or c

<220>
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<222> (448)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (451)
<223> n equals a,t,g, or c

<400> 371
ggcacaggat aattttaagc atttaaatgg aattnatcctt ttctactgta ttgatccaaa 60
tggttccaag cataaaagaa cggacagatc aattttatgt tgtttacgaa aaggagaatc 120
tggccagtca tggcaagggt taacaaaaga aagggcaaaag cttaattggc ttagtgctga 180
cttcaataat tgggaaagac tgggaagatg attcaaatga agacatgtct aattttgaat 240
cgtttctctg aggattcaca agacagtgat gatggnaaaa atgccagatc tgggagtaag 300
ggaatattgt ccntcacctg ggtttttgag gaaaggaaaa tnaactttct ctggcaagggt 360
tttcataat ttgngaggaa ttccccgagt ttgttagcnc cttaaaggcn gttatgctcg 420
tatttgnccc actntaacc ctttttnnca nccggtttgt ttttttaaaa gggcttc 477

<210> 372
<211> 443
<212> DNA
<213> Homo sapiens

<220>

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<220>
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<222> (67)
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<222> (74)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (107)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (116)
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<220>
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<222> (123)
<223> n equals a,t,g, or c

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<222> (171)
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<220>
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<222> (174)
<223> n equals a,t,g, or c

<220>
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<222> (220)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (222)
<223> n equals a,t,g, or c

<220>
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<222> (293)
<223> n equals a,t,g, or c

<220>
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<222> (314)
<223> n equals a,t,g, or c

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<222> (329)
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<220>
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<222> (335)
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<220>
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<222> (340)
<223> n equals a,t,g, or c

<220>
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<222> (351)
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<220>
<221> misc feature
<222> (364)
<223> n equals a,t,g, or c

<220>
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<222> (373)
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<220>
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<222> (407)
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<220>
<221> misc feature
<222> (411)
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<220>
<221> misc feature
<222> (426)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (430)

<223> n equals a,t,g, or c

<400> 372

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agaaganatc ctnnaccctt gtaggaatgt ttttgaaact aaatttnatg aacgtnaaat 120
ttncacgtgg ttattatgaa cttccttgtc gaagttgaaa ggtgaacaac nctnatattg 180
caaataccgt agagcttcag agtgcaagat tctccactgn angttgaggca ttcacaaatg 240
ttggatcttt cccaccgtgg gatgaagggt tcagaggcat tgcacccaaa atnaccggg 300
tgaacatacc cagnccaaag cccaggggna cattnatcgn ggacaggccc nccagaattt 360
ggcntgttct ttncacgttg gtaggtgtgg aacttggggg tgaattnatt ncttaaccga 420
attnnccgn ttccttaacc gag 443
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<210> 373

<211> 464

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (20)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (235)

<223> n equals a,t,g, or c

<400> 373

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gagacttggg gatggaaccg cacagagccg cgggcccttt gcagctgcga ttttegccct 120
acgttttcaa cggaggtact atactggcaa ttgctggaga agattttgca attgttgctt 180
ctgatactcg attgagtga gggttttcaa ttcatacgcg ggatagcccc aaatnttaca 240
aattaacaga caaacagtc attggatgca gcggttttca tggagactgt cttacgctga 300
caaagattat tgaagcaaga cttaaagatgt ataagcattc caataataag gccatgacta 360
cgggggcaat tgctgcaatg ctgtctacaa tcctgtattc aaggcgcttc tttccatact 420
atgttttcaa catcatcggt ggacttgatg aagaaggaaa gggg 464
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<210> 374

<211> 369

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (216)

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<220>
<221> misc feature
<222> (218)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (219)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (221)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (332)
<223> n equals a,t,g, or c

<220>
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<222> (357)
<223> n equals a,t,g, or c

<220>
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<222> (360)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (363)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (369)
<223> n equals a,t,g, or c

<400> 374
ggcacagcct ctacagccat gtattcggt cctggcagag acttggggat ggaaccgcac 60
agagccgcgg gccctttgca gctgcgattt tcgccctacg ttttcaacgg aggtactata 120
ctggcaattg ctggagaaga ttttgcaatt gttgcttctg atactcgatt gagtgaagg 180
tttcaattc atacgcggga tagcccaaa tgttgncnna ntaacagaca aaacagtcac 240
tggatgcagc ggttttcacg gagactgtct tacgctgaca aagattattg aagcaagact 300
aaagatgtat aagcattcca ataataaggc cntgactacg gggggcaatg ctggcangcn 360
gtnctacan 369

<210> 375

<211> 313
<212> DNA
<213> Homo sapiens

<220>
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<222> (32)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (249)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (259)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (268)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (293)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (308)
<223> n equals a,t,g, or c

<400> 375
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gtacacaacc gcccaactgc tggcggcaaa tgagcagaaa tttaagtgtg atccgctgtt 120
tctgcgtctc tttttccgtg agagctatcc cttcaccacg gaggaagtc tatctctcac 180
aaattccggg actggtaaac atggcgctgt acgtttcgcc gattgtttcc ggtgaagggt 240
atcccgttnc cctggcggtt tccacctntg aatttaaggc cgggataatg tcnaagcccg 300
aagcatgnaa gtg 313

<210> 376
<211> 375
<212> DNA
<213> Homo sapiens

<400> 376
cgggttccgg tgaccacgaa ggcggcaaa ggcacggaat ggaggaggtg cctcacgact 60
gtccaggggc cgacagcgcc caggcgggca gaggggcttc atgtcagga tgccccaacc 120
agcggctgtg cgcttctgga gcggggggcca ctccggacac ggctatagag gaaatcaaag 180

agaaaaatgaa gactgtaaaa cacaaaaatct tggattgtc tgggaaaggc ggtgttgga 240
aaagcacatt cagcgccac cttgccatg gcctagcaga ggatgaaaac acacagattg 300
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gacngagana gtncagaagc tgtgcccagg ggggcagntc ccattcctgc tntatngnac 120
tgaagtgcac acagacacca acaagnttgc ngaatttctg nangcagtgc tgtgccctcc 180
caggtacccc aanctggcag ctctgaaccc tnantccaac acagctgngc tgganatatt 240
tgncaaattn tctgcctaca tnnnnanttc aaaccacagna ctcaatgaca atctggagaa 300
nggactcctg aaagccctgn acgttttagn caattantta acatcccccc nctcagaaga 360
agtggatgan accagtgtg nagtgaaggt gtctctcaga agaagttnt ggatagcacg 420
agctcacctt gggg 434

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tatgcgactt accgcagcaa aaataaaggg aaagataagc gctcaataaa cctgtctgtt 120
ttccttaatt cntgtctggc tgataatcat cacctgcagg ttggctccaa ttatttgtat 180
attcataaaa tcgatggaaa aacttttctc tttacaaaaa caaatgacaa gagtctggtt 240
cagaagataa atcgctctaa agcttcagtt gaagatatta agaacagcct cgtngatgac 300
ggaaatcattg ggattcccat cttttttggt tgttgaaggc gacaccattg gtttttgcca 360
gaactgnittt tcgggncggc cacatncgnt tttgacaggt ttttttaatc ggggaaggga 420
ntgtccttaa ggcgtggggn gcngttcagt tggggccctg ttgggggggac cnccaaggng 480
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ctagaactag tggatcccc gggctgcagg aattcggcac gaggccatcc agactgagga 120
agacccggaa acttaggggc cacgtgagcc acggccacgg ccgcataggc aagcaccgga 180
agcaccgccg cgccgcgggt aatgctggtg gtctgcatca ccaccggatc aacttcgaca 240
aataccaccc aggtactttt gggaaagttg gtatgaagca ttaccactta aagaggaacc 300
agagcttctg cccaactgtc aaccttgaca aattgtggac tttggtcagt gaacagacac 360
gggtgaatgc tgctaaaaac aagactgggg ctgctcccat cattgatgtg gtgcgatcgg 420
gtactataa agttctggga aagggaaagc tcccaaagca gcctgtcatc gtgaaggcca 480
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<400> 380

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ccqctctada actagtggat cccccggggt gtaggaatgc ggcacgagcg caaagaggg 120
tggcgagaag aaaaagggcc gttctgcat caacgaaggn taacccgaga atacaccatc 180
aacattcaca agcgcaccca tggagtgggc ttcaagaagc gtgcacctcg ggcactcaaa 240
gagattcgga aatttgccat gaaggagatg ggaactccag atgtgcgcat tgacaccagg 300
ctcaacaaag ctgtctgggc caaaggaata aggaatgtgc cataccgaat ccgtgtgcgg 360
ctgtccagaa aacgtaatga ggatgaagat tcaccaaata agctatatac ttgggttacc 420
tatgtacctg ttaccacttt caaaatttct gtgctaaaca gtgttacagt cgccaagagc 480
ccataaaggg agccctcctg gaagtggatg aggccttggg tctcggtctt tcattgcttc 540
ctgagctgca gcagatgcct ttacaaccaa gct 573
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<210> 381

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<212> DNA

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<400> 381

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gcagcaatgg ccaagatcaa ggctcgagat cttcgggga agaagaagga ggagctgctg 180
aaacagctgg acgacctgaa ggtggagctg tcccagctgc gcgtcgccaa agtgacaggc 240
ggtgcggcct ccaagctctc taagatccga gtcgtccgga aatccattgc ccgtgttctc 300
acagttatta accagactca gaaagaaaac ctcaggaaat tctacaaggg caagaagtac 360
aagcccctgg acctgcggcc taagaagaca cgtgccatgc gccgccggt caacaagcac 420
gaggagaacc tgaagaccaa gaagcagcag cggaaggagc ggctgtaccc gctgcggaag 480
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accatccgca gagatgcccc tgctggccgc aaagtgggtc tcattgctgc nngcnggant 180
ggangtctcn ggggaaccaa gantgtgcag gagaaagaga actagtgtctg agggcctcaa 240
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ccggggccga ggcgcgggac tcgcgnaggc aaggccgagg ataaggagtg gatgcccgtc 180
accaagttag gccgcttggt caaggacatg aagatcaagt ccctggagga gatctatctc 240
ttctccctgc ccattaagga atcagagatc attgattctt cctgggggct ctctcaagga 300
tgagttttga agatatgccg tgcagaagca gaccctgccg gccacgcacc agttcaagca 360
ttnttgaac gggattaaat gccactcgtt tggtttaatg nccnagagtg gcacncatcc 420
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angagattaa ncagagacac aggcaattgt atgtcagcag ctngatttaa cccacctaaa 120
aggngcg 127

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aagctgtccc acttacagat gcacagcagg naagcacact ggtgagaaac cataccagtg 180
tgacttnaag gactgtgaac gangttttct cgttcagacc agctcaaaag ncaccaaagg 240
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gaccaacnga ngaccna 317

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cggcagcgcc atgagactcc tccccgctt gctgctgctt ctcttactcg tgttcctgc 180
cactgtcttg ttccgaggcg gccccagagg cttgttagca gtggcacaag atcttacaga 240
ggatgaagaa acagtagaag attccataat tgaggatgaa gatgatgaag ccgangtaga 300
agaagatgaa nccacagatt ttgtagaaga taaagaggaa gaagatgtgt ctggtgaanc 360
tgaaacttta ccgagtgcag atacnactat actgttttta aaggngnaga tttccgccca 420
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<210> 387
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<212> DNA
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gctttcctcc cccatctaca tcgatctgcg gggcatcgtg tctcgaccgc gtcttctgag 180
tcaggttgca gatattttat tccaaactgc ccaaaatgca ggcatcagtt ttgacaccgt 240
gtgtggagtg ccttatacag ctttgccatt ggctacagtt atctgttcaa ccaatcaaatt 300
tccaatgctt attanaagga aagaaacaaa ggattatgga actaagcgtc ttgtanaang 360
aatattaatc canganaaac tgtttaatca ttgaaatggt gtcccan 407
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<211> 244

<212> DNA

<213> Homo sapiens

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<400> 388

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tcaggcggcg catttttatt gctgtgttgc gctgtaattc ttctatttct gatgctgaat 120
caatgatgtc tgccatcttt cattaatccc tgaactgttg gttaatacgc ttgagggtga 180
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ttcc

244

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<212> DNA

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ctgncgcccg nctgatgcc agggaagaca gggcgacctg gaagtccaac tacttinctta 120
agatcatnca acgtattggg atgattatcc taaaatgggt tcnattgggt ggtagcgagt 180
acganatggt ggggcntcct anagntagta tggcgagcta ggtcccggc taatgttcc 239

<210> 390
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<220>
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<223> n equals a,t,g, or c

<220>
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<222> (374)
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<400> 390
tcaangcgca attaacccctc actaaaggga acaaaagctg ggaacgatct ggtntctctg 60
cgcgctgcnc gcacactgag gccgcccggg acaaagcccg gnntcggngc gacctttggt 120
cccgginctca gtgagcgagc gagcgcgag agagggagtg gccaaactna tcactagggg 180
ttccttgtag tnaatgatta acccgccatg ctacttngnc nacgtagcca tgggntacca 240
agctcgagct ctctagactc gacgcgcgta atacgactca ctatagggcg aatttgagct 300
ccaccgcggt tgcggccgct ctactagagt cgacctcatg gnttnncccc gaaacccgcn 360
aacaccgct gacncgcct ta 382

<210> 391
<211> 375
<212> DNA
<213> Homo sapiens

<220>
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<220>
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<222> (7)
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<220>
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<220>
<221> misc feature

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<220>
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<223> n equals a,t,g, or c

<220>
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<222> (138)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (146)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (159)
<223> n equals a,t,g, or c

<220>
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<222> (208)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (223)
<223> n equals a,t,g, or c

<220>
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<222> (261)
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<222> (269)
<223> n equals a,t,g, or c

<220>
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<222> (275)
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<220>

<221> misc feature

<222> (299)

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<220>

<221> misc feature

<222> (351)

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<220>

<221> misc feature

<222> (366)

<223> n equals a,t,g, or c

<220>

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<222> (370)

<223> n equals a,t,g, or c

<400> 391

tgcaanngaa tacacactaa ggacaagtgg actcacggtg cgccctcnga ctagtggtcc 60
cgggtgcagn tgccaggggtg gcctgagcga tctacggatg ggcngtatgg agtggangag 120
acgagatgcg ggtgttanag cagggnctga ccggagtgn acacatgagt gtcaggtgca 180
ggtagtccga gtcggcgaca tgagcctnga gtagagtcac cantcgatga gatctggagg 240
caactggcga gcaagaccgt ntgggtcant gtcantcang ctgttgcagg tgagagcant 300
gcactcgtcg agtggcgaga cagatcaatc tctgttagcg ggtggagggt nactcgcgc 360
tgtgnggtn cactg 375

<210> 392

<211> 121

<212> DNA

<213> Homo sapiens

<220>

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<220>

<221> misc feature

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (13)

<223> n equals a,t,g, or c

<220>
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<222> (56)
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<220>
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<220>
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<222> (113)
<223> n equals a,t,g, or c

<220>
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<222> (118)
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<220>
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<222> (120)
<223> n equals a,t,g, or c

<400> 392
gantcatcng agngtgtgga ttgagccgc cgcatttttt aaccctaaat ctcganatgc 60
atcgtgnttc ctgtccattg gactgtaagg tttatgtagg catcttgga acnatggan 120
a 121

<210> 393
<211> 83
<212> DNA
<213> Homo sapiens

<220>
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<222> (65)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (66)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (70)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (73)
<223> n equals a,t,g, or c

<400> 393
ggcagagaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60
aaaanncccn ggngggggcc ccc 83

<210> 394
<211> 218
<212> DNA
<213> Homo sapiens

<220>
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<222> (13)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (64)
<223> n equals a,t,g, or c

<400> 394
gtcggcgagc aangcgcccc gcacccccgc caggcgcatg tctgcacctc cgcttgccaa 60
aggncctcgg tcagcgactg gatgctcgcc atcaagggtcc agtggaagtt cttcaagagg 120
aaaggcgccc ccgccccagg cttccgcgcc cagcgctcgc cacgctcagt gcccgtttta 180
ccaataaaact gagcgacccc aaaaaaaaaa aaaaaaaag 218

<210> 395
<211> 83
<212> DNA
<213> Homo sapiens

<220>
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<222> (11)
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<220>
<221> misc feature
<222> (13)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (83)
<223> n equals a,t,g, or c

<400> 395
aattcggcac ngnaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60

aaaaaaaaaa aaaaaaaaaa aan

83

<210> 396

<211> 70

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (69)

<223> n equals a,t,g, or c

<400> 396

aattcggcac agaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 60
aaaaaaaaana 70

<210> 397

<211> 140

<212> DNA

<213> Homo sapiens

<220>

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<220>
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<222> (115)
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<220>
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<222> (139)
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aatTTgacca gagaacaaga ataaccCGgc CTCagCGccg ggTtttcttn gcctcangat 60
cgcccccaaa acanataacc aattgtattt atngaaaaat aaatagatac aannnactaa 120
acatagcaat tcagatctnt 140

<210> 398
<211> 157
<212> DNA
<213> Homo sapiens

<220>
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<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (65)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (121)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (122)
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<220>
<221> misc feature
<222> (123)
<223> n equals a,t,g, or c

<220>
<221> misc feature
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<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (134)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (150)
<223> n equals a,t,g, or c

<400> 398
aattcggc an agctcaagca gacggggctc aaggggggta catttaataa aaggatgaag 60
atggnaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa 120
nnncengggg gggnccccc ccccccttn cccctt 157

<210> 399
<211> 358
<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (84)
<223> n equals a,t,g, or c

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<221> misc feature
<222> (204)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (207)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (302)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (305)
<223> n equals a,t,g, or c

<220>
<221> misc feature

<222> (308)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (331)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (341)

<223> n equals a,t,g, or c

<400> 399

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gcaagcgcca tatgagcctg gcgncgcca tagcgaatcc tgttggtggc ttttggcct 120
attcccgccc ctgagtcttg ccgggatggc accgcccgca taggacttcc agggttggc 180
tgagtgggag ttcgactgct gggncctngta attctcgctt tgggggctgc tccttcagg 240
ctggggacac actggggccc gttgttcggt ctcccgtcct ccgacatctt gtctggaact 300
tncgncctngc agtttcata ggagttggag nctgtgcggc ntaatttttg tggaaaaa 358

<210> 400

<211> 399

<212> DNA

<213> Homo sapiens

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<222> (27)

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<222> (33)

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<220>

<221> misc feature

<222> (70)

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<220>
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<222> (83)
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<223> n equals a,t,g, or c

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<220>
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<220>
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<222> (216)
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<220>
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<222> (218)
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<220>
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<220>
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<220>
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<222> (349)
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<220>
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<222> (364)
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<220>
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<222> (382)
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aaaacccaan tcagagtatc canaaatcca agccagggtca aaaccaaacc gaaantntca 120
agcaatccaa atcaagtcaa aaacaaaaac caaagtgccg gtacaggcnt nccgtgggtg 180
atcaggccac ccttcactc aaatggagtg ggnaantncc aaagactagt nttaccaant 240
ttcanatntc cggantccaa gngcctgtnc ctcccagng ttnagccgct gnattgatcc 300
tctgtggggg cctgcnaaac gccantctgg cgaggtgttc cactggggna attgcctacc 360
cggnagtgtc ctcaggttct gngtccctca agctggcca 399

<210> 401
<211> 189
<212> DNA
<213> Homo sapiens

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<220>
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<222> (11)
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<220>
<221> misc feature
<222> (162)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (165)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (166)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (187)
<223> n equals a,t,g, or c

<400> 401
naattcggca nagcaaacca caccttctct ttcttatgtc tttttactac aaactacaag 60
acaattgttg aaacctgcta tacatgttta ttttaataaa ttgatggcaa aaaaaaaaaa 120
aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa anccnngggg ggggcccccc 180
ccccccntt 189

<210> 402
<211> 174
<212> DNA
<213> Homo sapiens

<220>
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<222> (10)
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<220>
<221> misc feature
<222> (73)
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<220>
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<222> (103)
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<220>
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<220>
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<222> (130)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (132)
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<220>
<221> misc feature
<222> (146)
<223> n equals a,t,g, or c

<220>
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<222> (149)
<223> n equals a,t,g, or c

<220>
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<222> (167)
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<400> 402
aatcggcan agctgaggca ggagaatcgc ttgaattcgg gaggcagagc tgagatcaca 60
cctctgacac tcnagcctgg gtgacagagc gagactccgt ctnaggnaag gaaaaaaaaa 120
aaaaaaaaan cncggggggg gccccngtnc ccaattggcc ctatagnggg tcgt 174

<210> 403
<211> 263
<212> DNA
<213> Homo sapiens

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<221> misc feature
<222> (231)
<223> n equals a,t,g, or c

<220>
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<220>
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<222> (242)
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<220>
<221> misc feature
<222> (252)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (260)
<223> n equals a,t,g, or c

<400> 403

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ctgggaccac aaggaggag actgcacccc actgcctctg ggccctggct gtgggcagag 120
gccaccgtgt gtgtcccgag taaccgtgcc gttgtcgtgt gatgccataa gcgtctgtgc 180
gtggagtccc caatgaaacc tgtggtcctg cctgggcaaa aaaaaaaaaa naaaanaaaa 240
anaaaagaaa anaaaaaaan aaa 263

<210> 404

<211> 478

<212> DNA

<213> Homo sapiens

<220>

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<222> (159)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (259)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (427)

<223> n equals a,t,g, or c

<400> 404

tcgacccacg cgtccggggg ctgcagcatg ttgctgagga gtgaggaata gttgagcccc 60
aagtcctgaa gaggcgggcc agccaggctg acatctgtgt ttcaagtggg gctcgccatg 120
ccgggggttc ataggctact ggctctccaa gtgccagang tgggcagggt gtggcactga 180
gcccccccaa cactgtgccc tgggtggagaa agcactgacc tgtcatgccc cctctaaacc 240
tcctcttctg acgtgcctnt tgcaccctc ccattaggac aatcagtccc ctcccatctg 300
ggagtccctt tttcttttct accctagcca ttccctgtac ccagccatct gcccaagggt 360
gccccctcct ctcccatccc cctgccctcg tgggcagccc ggctggtttt gtaaatgtgg 420
gttgtgnaca gtgatttttt cttgtattta aaaaaggcca gcattgtggt tcattaaa 478

<210> 405

<211> 223

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (147)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (158)

<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (172)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (217)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (223)
<223> n equals a,t,g, or c

<400> 405
agacagcagg acggtggcca tggaagtcgg aatccgctaa ggagtgtgta acaactcacc 60
tgccgaatca actagccctg aaaatggatg gcgctggagc gtcggggcca taccggtccg 120
tcgccggcag tcgagagtgg acggggancgg cggggggcngc gcgcgcgcgc gncgtgatgg 180
tgtgcgtcgg agggcggcgg cggcggcggg ggtgtgnggt ccn 223

<210> 406
<211> 104
<212> DNA
<213> Homo sapiens

<220>
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<220>
<221> misc feature
<222> (37)
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<220>
<221> misc feature
<222> (81)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (93)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (103)
<223> n equals a,t,g, or c

<400> 406
cccacgentc cgccgacagc agcagcctca ccatgangtt gctgatgggc ctcatgctgg 60
cggccctctc ccagcactgc nacgcaggct ctngctgccc ctna 104

<210> 407
<211> 66
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (17)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (21)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (57)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (66)
<223> n equals a,t,g, or c

<400> 407
gccctatagt gagtctngta ncaattcact ggccgctcgtt ttacaacgtc gtgacngnga 60
aaactn 66

<210> 408
<211> 278
<212> DNA
<213> Homo sapiens

<220>
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<222> (6)
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<220>
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<222> (19)
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<220>
<221> misc feature

<222> (252)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (275)
<223> n equals a,t,g, or c

<400> 408
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gattacaggc atgagccaat atgaccagct caaacatctt ctttttaa at gtcagaagca 120
tgtatagtga ttatttctta ttttttcccc cttgatccat ctcaccagat gtttgttgat 180
tttataagaa ttttcaaact accagcttct ggctttgttg aacttgggat ttctgtttca 240
ctaattttct tntcctgtgc ttgtacttac ttgntggtg 278

<210> 409
<211> 168
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (16)
<223> n equals a,t,g, or c

<220>
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<222> (38)
<223> n equals a,t,g, or c

<220>
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<222> (127)
<223> n equals a,t,g, or c

<220>
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<222> (140)
<223> n equals a,t,g, or c

<220>
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<222> (143)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (145)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (167)
<223> n equals a,t,g, or c

<400> 409
aataaaactc taaaangatc actataaaaa aagcaggac gcctgcaggt accggtccgg 60
aattcccggg tcgaccacg cgtccgacgg ctgcgagaag acgacagaag ggcacggctg 120
cgagaanacg acagaagggn gcnantgaaa gaaggcggca gaaaggnt 168

<210> 410
<211> 415
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (307)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (347)
<223> n equals a,t,g, or c

<400> 410
tgaataccta agatttctgt cttgggggttt ttggtgcatg cagttgatta cttcttattt 60
ttcttaccac ttgtgaatgt tggtgtgaaa caattaatga agcttttgaa tcatccctat 120
tctgtgtttt atctagtcac ataaatggat taattactaa tttcagttga gaccttctaa 180
ttggttttta ctgaaacatt gagggaacac aaatttatgg gcttcctgat gatgattctt 240
ctaggcatca tgctctatag ttgtcatcc ctgatgaatg taaaattaca ctgttcacaa 300
aggtttngtc tcctttccac tgctattaat catggtcact ctcccnaaa tattatattt 360
ttctatttaa aagaaaaaaa tggaaaaaaa ttacaaggca atggaaacta ttata 415

<210> 411
<211> 636
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (383)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (512)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (519)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (544)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (547)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (583)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (599)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (603)

<223> n equals a,t,g, or c

<400> 411

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gcagatcaga cgtggcgacc cgctgaattt aagcatatta gtcagcggag gagaagaaac 60
taaccaggat tccctcagta acggcgagtg aacaggggaag agcccagcgc cgaatccccg 120
ccccgcggcg gggcgcgagg catgtggcgt acggaagacc cgctccccgg cgccgctcgt 180
ggggggccca agtccttctg atcgaggccc agcccgtgga cgggtgtgagg ccggtagcgg 240
cccccgggcg gccggggccc ggtcttcccg gagtccgggtt gcttggggaat gcagcccaaa 300
gcgggtggta aactccatct aaggctaaat ccccttgtaa atttaactgt tagtccaaag 360
aggaacagct ctttgacac tangaaaaaa cctttagag agagtaaaaa atttaacacc 420
catagtaggc ctaaaagcag ccaccaatta agaaagcgtt caagctcaac acccactacc 480
taaaaaatcc caaacatata actgaactcc tnacaccna ttggaccaat ctatcaccct 540
atanaanaac taatggtagt ataagtaaca tgaaaacatt ctncctcgca taagcctgng 600
tanattaata cacttgaact gaccattaac aggcca 636
```

<210> 412

<211> 182

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (129)

<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (166)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (169)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (170)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (172)
<223> n equals a,t,g, or c

<400> 412
ccattgattt ttatcaatag tcgtattcat acggatagtc ctggtattgt tccatcacat 60
tctgaggatg ctcttcgaac tcttcaaatt cttcttccat atatcacctt aaatagtga 120
ttgcgggtant aaagattgtg cctgtctttt aaccacatca ggctcngann gntctcgtga 180
ac 182

<210> 413
<211> 387
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (157)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (253)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (317)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (323)
<223> n equals a,t,g, or c

<220>

<221> misc feature
<222> (349)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (351)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (364)
<223> n equals a,t,g, or c

<400> 413
tcgacccacg cgtccgccca cgcgtccgcc aagaccaccc tcctttcatt tgctagaagg 60
actcactaga ctcaggaaaag ctgttaggct cacagttaca gtttattaca gtaaaaggac 120
agagattaag atcagcaaag ggaggagggt cacagcnacg ttccacgaca gatgaggcga 180
cggcttccat ctgccctctc ccagtggagc catataggca gcacctgatt ctcacagcaa 240
catgtgacaa canccaagaa gtactgccaa tactgccaac cagagcagct tcactcggag 300
atctttgtgt tccaganttt ttngttgtgc ttggagacag ggtctgggnc ngtttgggca 360
gacnaagagt acatggtgga gattcac 387

<210> 414
<211> 276
<212> DNA
<213> Homo sapiens

<220>
<221> misc feature
<222> (60)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (186)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (195)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (237)
<223> n equals a,t,g, or c

<220>
<221> misc feature
<222> (260)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (266)

<223> n equals a,t,g, or c

<400> 414

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gcaaagggtcc atactgggtta cttgggtttca ttgccaccac ttagtggatg ttcagtttan 60
aaccatttttg tctgctccct ctggaagcct tgcgcatagc ttactttgta attgttgag 120
aataactgct gaatttttag ctgttttgag ttgattcgca ccactgcacc acaactcact 180
atgaanacta tttancttat ttattatctt gtgaaaagta taccatgaaa attttgnatca 240
tactgtattt atcaagtatn attaanagca ctagat 276
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<210> 415

<211> 192

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (78)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (88)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (99)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (145)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (150)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (164)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (168)

<223> n equals a,t,g, or c

<400> 415

aaaagattgg actaagacac tggccatacc actggacagg gttatgttaa cacctgaaat 60
tgctgggtct tgagagancc caacgcantt ctgggagang gaccacattg gggggtaggt 120
ccacgggctt ggtgatagaa ttatntctcn atcgacttct tgantgcnat atgaactgta 180
acatttgctt ag 192

<210> 416

<211> 439

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (7)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (64)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (406)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (417)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (421)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (431)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (434)

<223> n equals a,t,g, or c

<400> 416

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gcgagantnc gacagaaggg tacggctgcg agagacgaca gaagggtacg gctgcgagaa 60
gacnacagaa ggggtacggct gcgagaagac gacagaaggg tacggctgcg agaagacgac 120
agaagggtac ggctgcgaga agacgacaga aggtacggct gcgagaagac gacagaagga 180
tacggctgcg agaagacgac agaagggaga atcttagttc aactttaaat ttgcccacag 240
aaccctctaa atccccttgt aaatttaact gttagtccaa agaggaacag ctctttggac 300
actaggaaaa aacctgttag agagagtaaa aaatttaaca cccatagtag gcctaaaagc 360
agccaccaat taagaaagcg ttcaaagctc aacacccact acccnaaaa taaaaanaaa 420
naaaaacccg nggncgcgt 439
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<210> 417

<211> 155

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (9)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (84)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (122)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (123)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (143)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (153)

<223> n equals a,t,g, or c

<400> 417

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gacatcttnt tggtttttat tttgaaacaa tttttaggct tgttccgggg gtctctgtgc 60
tgctgtact gtattgacct gttntatagg tgcccttttta ttaaaaagaa aattcaaaaa 120
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annaaaaaaaa aaattaataa aaaaaaaaaa aanca

155

<210> 418

<211> 291

<212> DNA

<213> Homo sapiens

<220>

<221> misc feature

<222> (285)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (286)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (288)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (289)

<223> n equals a,t,g, or c

<220>

<221> misc feature

<222> (291)

<223> n equals a,t,g, or c

<400> 418

gaaaaaagaa atccatatct taaagaaaca gctttcaagt gcctttctgc agtttttcag 60
gagcgcaaga tagatttgga ataggaataa gctctagttc ttaacaaccg acactcctac 120
aagatttaga aaaaagttaa caacataatc tagtttacag aaaaatcttg tgctagaata 180
ctttttaaaa ggtattttga ataccattaa aactgctttt tttttccag caagtatcca 240
accaacttgg ttctgcttca ataaatcttt ggaaaaacta atttnnanna n 291

<210> 419

<211> 340

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (315)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 419

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Xaa | Asp | Trp | Phe | Leu | Trp | Tyr | Val | Lys | Lys | Cys | Gly | Gly | Thr | Thr |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Arg | Ile | Ile | Ser | Thr | Thr | Asn | Gly | Gly | Gln | Glu | Arg | Lys | Phe | Val | Gly |
| | | | 20 | | | | | 25 | | | | | | 30 | |
| Gly | Ser | Gly | Gln | Val | Ser | Glu | Arg | Ile | Met | Asp | Leu | Leu | Gly | Asp | Arg |
| | | 35 | | | | | 40 | | | | | | 45 | | |
| Val | Lys | Leu | Glu | Arg | Pro | Val | Ile | Tyr | Ile | Asp | Gln | Thr | Arg | Glu | Asn |
| | 50 | | | | | 55 | | | | | | 60 | | | |
| Val | Leu | Val | Glu | Thr | Leu | Asn | His | Glu | Met | Tyr | Glu | Ala | Lys | Tyr | Val |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |
| Ile | Ser | Ala | Ile | Pro | Pro | Thr | Leu | Gly | Met | Lys | Ile | His | Phe | Asn | Pro |
| | | | 85 | | | | | | 90 | | | | | 95 | |
| Pro | Leu | Pro | Met | Met | Arg | Asn | Gln | Met | Ile | Thr | Arg | Val | Pro | Leu | Gly |
| | | 100 | | | | | | 105 | | | | | | 110 | |
| Ser | Val | Ile | Lys | Cys | Ile | Val | Tyr | Tyr | Lys | Glu | Pro | Phe | Trp | Arg | Lys |
| | 115 | | | | | | 120 | | | | | | 125 | | |
| Lys | Asp | Tyr | Cys | Gly | Thr | Met | Ile | Ile | Asp | Gly | Glu | Glu | Ala | Pro | Val |
| 130 | | | | | | 135 | | | | | 140 | | | | |
| Ala | Tyr | Thr | Leu | Asp | Asp | Thr | Lys | Pro | Glu | Gly | Asn | Tyr | Ala | Ala | Ile |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |
| Met | Gly | Phe | Ile | Leu | Ala | His | Lys | Ala | Arg | Lys | Leu | Ala | Arg | Leu | Thr |
| | | | 165 | | | | | | 170 | | | | | 175 | |
| Lys | Glu | Glu | Arg | Leu | Lys | Lys | Leu | Cys | Glu | Leu | Tyr | Ala | Lys | Val | Leu |
| | | 180 | | | | | | 185 | | | | | 190 | | |
| Gly | Ser | Leu | Glu | Ala | Leu | Glu | Pro | Val | His | Tyr | Glu | Glu | Lys | Asn | Trp |
| | 195 | | | | | | 200 | | | | | | 205 | | |
| Cys | Glu | Glu | Gln | Tyr | Ser | Gly | Gly | Cys | Tyr | Thr | Thr | Tyr | Phe | Pro | Pro |
| 210 | | | | | | 215 | | | | | | 220 | | | |
| Gly | Ile | Leu | Thr | Gln | Tyr | Gly | Arg | Val | Leu | Arg | Gln | Pro | Val | Asp | Arg |
| 225 | | | | | 230 | | | | | 235 | | | | | 240 |
| Ile | Tyr | Phe | Ala | Gly | Thr | Glu | Thr | Ala | Thr | His | Trp | Ser | Gly | Tyr | Met |
| | | | 245 | | | | | | 250 | | | | | 255 | |

368

Glu Gly Ala Val Glu Ala Gly Glu Arg Ala Ala Arg Glu Ile Leu His
 260 265 270

Ala Met Gly Lys Ile Pro Glu Asp Glu Ile Trp Gln Ser Glu Pro Glu
 275 280 285

Ser Val Asp Val Pro Ala Gln Pro Ile Thr Thr Thr Phe Leu Glu Arg
 290 295 300

His Leu Pro Ser Val Pro Gly Leu Leu Arg Xaa Ile Gly Leu Thr Thr
 305 310 315 320

Ile Phe Ser Ala Thr Ala Leu Gly Phe Leu Ala His Lys Arg Gly Leu
 325 330 335

Leu Val Arg Val
 340

<210> 420

<211> 111

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (48)

<223> Xaa equals any of the naturally occurring L-amino acids .

<400> 420

Thr Arg Asp Leu Val Ser Phe Ile Ser Gly Ile Arg Leu Tyr Asn Leu
 1 5 10 15

Met Leu Ser Val Leu Arg His Lys Arg Gln Asn Val Ala Tyr Phe Arg
 20 25 30

Ile Cys Phe Phe Ile Glu Val Ser Gly Ile Leu Ser Lys Ile Val Xaa
 35 40 45

Ser Arg His Cys Ser Leu Cys Ser Ser Gly Thr Ser Cys Pro Leu Leu
 50 55 60

Ser Leu Gln Ala Thr Gly Asn Ala Ser Val Leu Val Ser Trp Arg Lys
 65 70 75 80

Ile Thr Trp Gly Glu Gly Thr Ser Cys Gly Lys Ser Lys Cys Arg Tyr
 85 90 95

Glu Met Arg Arg Leu Pro Gln Leu Lys Val Asp Lys Ser Ala Leu

100

105

110

<210> 421

<211> 61

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 421

Xaa Ile Trp Cys Ile Ile Cys Lys Glu Ser Lys Met Met Ser Phe Pro
 1 5 10 15

Arg Gly Met Asn Leu Arg Asn Ala Phe Asp Gly Asp Val Ser Val Thr
 20 25 30

Leu Cys Tyr Ser Gly Ser Ser Asn Asn Ser Lys Ala Asn Tyr Ser Lys
 35 40 45

Cys Lys Ile Phe Leu Phe Pro Arg Phe Thr Phe Val Trp
 50 55 60

<210> 422

<211> 51

<212> PRT

<213> Homo sapiens

<400> 422

Thr His Ala Tyr Cys Ser Asn Leu Ser Phe Arg Leu Tyr Asp Gln Trp
 1 5 10 15

Arg Ala Trp Met Gln Lys Ser His Lys Thr Arg Asn Gln His Arg Thr
 20 25 30

Arg Gly Ser Cys Pro Arg Ala Asp Gly Ala Arg Arg Glu Val Leu Pro
 35 40 45

Asp Lys Leu
 50

<210> 423

<211> 246

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (71)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (101)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (117)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (147)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 423

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Arg | Asn | Asp | Met | Lys | Ala | Asp | Cys | Ile | Leu | Tyr | Tyr | Gly | Phe | Gly |
| 1 | | | | 5 | | | | | | 10 | | | | | 15 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ile | Phe | Arg | Ile | Ser | Ser | Met | Val | Val | Met | Glu | Asn | Val | Gly | Gln |
| | | | 20 | | | | | | 25 | | | | | 30 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Lys | Leu | Tyr | Glu | Met | Val | Ser | Tyr | Cys | Gln | Asn | Ile | Ser | Lys | Cys |
| | | 35 | | | | | | | 40 | | | | | 45 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Arg | Val | Leu | Met | Ala | Gln | His | Phe | Asp | Glu | Val | Trp | Asn | Ser | Glu |
| | | 50 | | | | | | 55 | | | | | | 60 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Cys | Asn | Lys | Met | Cys | Xaa | Asn | Cys | Cys | Lys | Asp | Ser | Ala | Phe | Glu |
| 65 | | | | | | 70 | | | | | 75 | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Lys | Asn | Ile | Thr | Glu | Tyr | Cys | Arg | Asp | Leu | Ile | Lys | Ile | Leu | Lys |
| | | | | 85 | | | | | | 90 | | | | | 95 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Ala | Glu | Gly | Xaa | Gly | Met | Glu | Lys | Leu | Thr | Pro | Ile | Gly | Asn | Trp |
| | | | 100 | | | | | | 105 | | | | | | 110 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Asp | Ser | Trp | Xaa | Gly | Lys | Gly | Ala | Ala | Lys | Leu | Arg | Val | Ala | Gly |
| | | | 115 | | | | | 120 | | | | | | | 125 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Val | Ala | Pro | Thr | Leu | Pro | Arg | Glu | Asp | Leu | Glu | Lys | Ile | Ile | Ala |
| | | | | | | | | | | 135 | | | | | 140 |

371

His Phe Xaa Ile Gln Gln Tyr Leu Lys Glu Asp Tyr Ser Phe Thr Ala
 145 150 155 160

Tyr Ala Thr Ile Ser Tyr Leu Lys Ile Gly Pro Lys Ala Asn Leu Leu
 165 170 175

Asn Asn Glu Ala His Ala Ile Thr Met Gln Val Thr Lys Ser Thr Gln
 180 185 190

Asn Ser Phe Arg Ala Glu Ser Ser Gln Thr Cys His Ser Glu Gln Gly
 195 200 205

Asp Lys Lys Met Glu Glu Lys Asn Ser Gly Asn Phe Gln Lys Lys Ala
 210 215 220

Ala Asn Met Leu Gln Gln Ser Gly Ser Lys Asn Thr Gly Ala Lys Lys
 225 230 235 240

Arg Lys Ile Asp Asp Ala
 245

<210> 424

<211> 109

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 424

Asp His Trp Pro Arg Pro Glu Trp Leu Pro Cys Thr Ser Trp Arg Arg
 1 5 10 15

Ala Ser Cys Leu Asn His Val Asn Cys His His Leu Ala Thr Pro Ala
 20 25 30

Pro Ala Ser Ala Leu Pro Pro Phe Pro Pro Ser Trp Ser Gly Gly Tyr
 35 40 45

Arg Ser Leu Gly Pro Thr Leu Ala Pro Leu Ser Pro Ala Ser Val Cys
 50 55 60

Leu Thr Val Phe Pro Pro Leu Pro Gln Leu Arg Cys Xaa Pro Gln Ala
 65 70 75 80

Trp Cys Cys Leu Gly Gly Leu Gly Glu Gly Val Cys Gly Gly Gly Arg
 85 90 95

Arg Val Lys Thr Glu Ala Arg Cys Gln Asn Gly Leu Glu
 100 105

<210> 425
 <211> 57
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (5)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (49)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 425
 Gly Ser Glu Thr Xaa Lys Tyr Leu Val Glu Asp Lys Arg Leu Gly Leu
 1 5 10 15

Tyr Thr Trp Leu Cys Thr Asp Leu Leu Ser His Ile Gly Asn His His
 20 25 30

Thr Leu Gln Gly Ile Ser Phe Ile Cys Lys Met Gln Arg Leu Val Leu
 35 40 45

Xaa Asn His Thr Asn Phe Phe Val Leu
 50 55

<210> 426
 <211> 99
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (96)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 426
 Phe Gly Thr Ser Gly Asp Gly Gly Gly Ser Lys Met Ala Gln Ala Ile
 1 5 10 15

Phe Glu Ala Leu Glu Gly Met Asp Asn Gln Thr Val Leu Ala Val Gln

373

20 25 30
 Ser Leu Leu Asp Gly Gln Gly Ala Val Pro Asp Pro Thr Gly Gln Ser
 35 40 45
 Val Asn Ala Pro Pro Ala Ile Gln Pro Leu Asp Asp Glu Asp Val Phe
 50 55 60
 Leu Cys Gly Lys Cys Lys Lys Gln Phe Asn Ser Leu Pro Ala Phe Met
 65 70 75 80
 Thr His Lys Arg Glu Gln Cys Gln Gly Asn Ala Pro Ala Leu Ala Xaa
 85 90 95
 Val Ser Leu

<210> 427

<211> 55

<212> PRT

<213> Homo sapiens

<400> 427

Asn Ser Asn Ser Ser Ile Phe Ser Leu Val Ser Val Lys Cys Asp Lys
 1 5 10 15
 Ser Thr Tyr Phe Lys Leu Phe Ser Ala Leu Gly Tyr Ser Ser Asn Lys
 20 25 30
 Asn Thr Asn Leu Trp Val Phe Lys Lys Thr Trp Arg Ile Asn Ser Tyr
 35 40 45
 Phe Lys Arg Ser Lys Lys Lys
 50 55

<210> 428

<211> 54

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 428

His Thr Leu Ser Asn Leu Glu Phe Ala Gln Lys Val Glu Pro Cys Asn

374

1 5 10 15
 Asp His Val Arg Ala Lys Leu Ser Trp Ala Lys Lys Arg Asp Glu Asp
 20 25 30
 Asp Val Pro Thr Val Pro Ser Thr Xaa Gly Glu Glu Arg Leu Tyr Asn
 35 40 45
 Pro Phe Leu Arg Val Ala
 50

<210> 429
 <211> 39
 <212> PRT
 <213> Homo sapiens

<400> 429
 Arg Gln Thr Lys Val Asn Leu Lys Glu Thr Arg Ser Phe Glu Ile Ile
 1 5 10 15
 Val Trp Gly Phe Tyr Lys Ser Asn Tyr Cys His Leu His Pro Asp Ser
 20 25 30
 Phe Lys Leu Leu Ile His Pro
 35

<210> 430
 <211> 133
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (81)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (85)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 430
 Ala Arg Ala Pro Arg Val Pro Pro Ala Pro His Thr Pro Ser Lys Met
 1 5 10 15
 Gly Lys Glu Lys Thr His Ile Asn Ile Val Val Ile Gly His Val Asp
 20 25 30

375

Ser Gly Lys Ser Thr Thr Thr Gly His Leu Ile Tyr Lys Cys Gly Gly
 35 40 45

Ile Asp Lys Arg Thr Ile Glu Lys Phe Glu Lys Glu Ala Ala Glu Met
 50 55 60

Gly Lys Gly Ser Phe Lys Tyr Ala Trp Val Leu Asp Lys Leu Lys Ala
 65 70 75 80

Xaa Val Ser Ala Xaa Ile Thr Ile Asp Ile Ser Leu Trp Lys Phe Glu
 85 90 95

Thr Thr Lys Tyr Tyr Ile Thr Ile Ile Asp Ala Pro Gly His Arg Asp
 100 105 110

Phe Ile Lys Asn Met Ile Thr Gly Thr Ser Gln Ala Asp Cys Ala Val
 115 120 125

Leu Ile Val Ala Ala
 130

<210> 431

<211> 190

<212> PRT

<213> Homo sapiens

<400> 431

Leu Cys Trp Ala Arg Pro Leu Pro Ser Gly Pro Val Leu Leu Ala Ala
 1 5 10 15

Asn Lys Asp Ser Ser Trp Cys Pro Thr Cys Leu Val His Cys Cys Val
 20 25 30

Asn Pro Gly Gly Ser Gly His Arg Arg Gln Pro Arg Pro Arg Val Gln
 35 40 45

Glu Lys Cys Ser Leu Glu Ala Arg Thr Thr Ala Ser His Trp Gly Arg
 50 55 60

Arg Gly Pro Arg Thr Thr Ser Ala Ser Tyr Leu Pro Ala Ser Ala Arg
 65 70 75 80

Gly Pro Arg Asp Ala Val Leu Phe Gln Pro Pro Ala Leu Gly Arg Gly
 85 90 95

His Ala Ser Arg Ile Gln Gly Ala Gly Gly Leu Ser Thr Ala Arg Thr
 100 105 110

376

Cys Leu Leu Ala Ala Ala Val Gly Glu His Gly Gly Cys Gln Arg
 115 120 125
 Leu Leu Trp Lys Val Ala Ala Ser Glu Met Ala Gly Ala Ala Gly Val
 130 135 140
 Arg Leu His Thr Ala Gln Val Ser Ser Gly Arg Leu Ser Trp Gly Gly
 145 150 155 160
 Ser Ser Ser Ala Glu Gly Trp Trp Gly Val Gln Ser Val Ile Leu Gly
 165 170 175
 Ala Val Cys Pro Thr Pro Ala Trp Gly Pro His Phe Arg Arg
 180 185 190

<210> 432
 <211> 310
 <212> PRT
 <213> Homo sapiens

<400> 432
 Gly Pro His Gly Asn Gly Glu Val Arg Trp Pro Leu Pro Pro Pro Pro
 1 5 10 15
 Pro Arg Phe Val Ala Arg Arg Lys Met Ala Asp Leu Glu Glu Gln Leu
 20 25 30
 Ser Asp Glu Glu Lys Val Arg Ile Ala Ala Lys Phe Ile Ile His Ala
 35 40 45
 Pro Pro Gly Glu Phe Asn Glu Val Phe Asn Asp Val Arg Leu Leu Leu
 50 55 60
 Asn Asn Asp Asn Leu Leu Arg Glu Gly Ala Ala His Ala Phe Ala Gln
 65 70 75 80
 Tyr Asn Leu Asp Gln Phe Thr Pro Val Lys Ile Glu Gly Tyr Glu Asp
 85 90 95
 Gln Val Leu Ile Thr Glu His Gly Asp Leu Gly Asn Gly Lys Phe Leu
 100 105 110
 Asp Pro Lys Asn Arg Ile Cys Phe Lys Phe Asp His Leu Arg Lys Glu
 115 120 125
 Ala Thr Asp Pro Arg Pro Cys Glu Val Glu Asn Ala Val Glu Ser Trp
 130 135 140
 Arg Thr Ser Val Glu Thr Ala Leu Arg Ala Tyr Val Lys Glu His Tyr

377

145 150 155 160
 Pro Asn Gly Val Cys Thr Val Tyr Gly Lys Lys Ile Asp Gly Gln Gln
 165 170 175
 Thr Ile Ile Ala Cys Ile Glu Ser His Gln Phe Gln Ala Lys Asn Phe
 180 185 190
 Trp Asn Gly Arg Trp Arg Ser Glu Trp Lys Phe Thr Ile Thr Pro Ser
 195 200 205
 Thr Thr Gln Val Val Gly Ile Leu Lys Ile Gln Val His Tyr Tyr Glu
 210 215 220
 Asp Gly Asn Val Gln Leu Val Ser His Lys Asp Ile Gln Asp Ser Leu
 225 230 235 240
 Thr Val Ser Asn Glu Val Gln Thr Ala Lys Glu Phe Ile Lys Ile Val
 245 250 255
 Glu Ala Ala Glu Asn Glu Tyr Gln Thr Ala Ile Ser Glu Asn Tyr Gln
 260 265 270
 Thr Met Ser Asp Thr Thr Phe Lys Ala Leu Arg Arg Gln Leu Pro Val
 275 280 285
 Thr Arg Thr Lys Ile Asp Trp Asn Lys Ile Leu Ser Tyr Lys Ile Gly
 290 295 300
 Lys Glu Met Gln Asn Ala
 305 310

<210> 433

<211> 289

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (287)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (288)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 433

Gln Ser Cys Thr Ser Gly Ser Ser Lys Pro Asn Ser Pro Ser Ile Ser

378

1 5 10 15
 Pro Ser Ile Leu Ser Asn Thr Glu His Lys Arg Gly Pro Glu Val Thr
 20 25 30
 Ser Gln Gly Val Gln Thr Ser Ser Pro Ala Cys Lys Gln Glu Lys Asp
 35 40 45
 Asp Lys Glu Glu Lys Lys Asp Ala Ala Glu Gln Val Arg Lys Ser Thr
 50 55 60
 Leu Asn Pro Asn Ala Lys Glu Phe Asn Pro Arg Ser Phe Ser Gln Pro
 65 70 75 80
 Lys Pro Ser Thr Thr Pro Thr Ser Pro Arg Pro Gln Ala Gln Pro Ser
 85 90 95
 Pro Ser Met Val Gly His Gln Gln Pro Thr Pro Val Tyr Thr Gln Pro
 100 105 110
 Val Cys Phe Ala Pro Asn Met Met Tyr Pro Val Pro Val Ser Pro Gly
 115 120 125
 Val Gln Pro Leu Tyr Pro Ile Pro Met Thr Pro Met Pro Val Asn Gln
 130 135 140
 Ala Lys Thr Tyr Arg Ala Gly Lys Val Pro Asn Met Pro Gln Gln Arg
 145 150 155 160
 Gln Asp Gln His His Gln Ser Ala Met Met His Pro Ala Ser Ala Ala
 165 170 175
 Gly Pro Pro Ile Ala Ala Thr Pro Pro Ala Tyr Ser Thr Gln Tyr Val
 180 185 190
 Ala Tyr Ser Pro Gln Gln Phe Pro Asn Gln Pro Leu Val Gln His Val
 195 200 205
 Pro His Tyr Gln Ser Gln His Pro His Val Tyr Ser Pro Val Ile Gln
 210 215 220
 Gly Asn Ala Arg Met Met Ala Pro Pro Thr His Ala Gln Pro Gly Leu
 225 230 235 240
 Val Ser Ser Ser Ala Thr Gln Tyr Gly Ala His Glu Gln Thr His Ala
 245 250 255
 Met Tyr Ala Cys Pro Lys Leu Pro Tyr Asn Lys Glu Thr Ser Pro Ser
 260 265 270
 Phe Tyr Phe Ala Ile Ser Thr Gly Ser Leu Ala Gln Gln Tyr Xaa Xaa

379

275

280

285

Pro

<210> 434

<211> 147

<212> PRT

<213> Homo sapiens

<400> 434

Lys Val Thr Pro Asp Leu Lys Pro Thr Glu Ala Ser Ser Ser Ala Phe
 1 5 10 15

Arg Leu Met Pro Ala Leu Gly Val Ser Val Ala Asp Gln Lys Gly Lys
 20 25 30

Ser Thr Val Ala Ser Ser Glu Ala Lys Pro Ala Ala Thr Ile Arg Ile
 35 40 45

Val Gln Gly Leu Gly Val Met Pro Pro Lys Ala Gly Gln Thr Ile Thr
 50 55 60

Val Ala Thr His Ala Lys Gln Gly Ala Ser Val Ala Ser Gly Ser Gly
 65 70 75 80

Thr Val His Thr Ser Ala Val Ser Leu Pro Ser Met Asn Ala Ala Val
 85 90 95

Ser Lys Thr Val Ala Val Ala Ser Gly Ala Ala Arg Pro Pro Ser Ala
 100 105 110

Ser Ala Gln Glu Pro Pro Pro Cys Gly Arg Ser Leu Ser Ala Pro Arg
 115 120 125

Leu Cys Pro Arg Pro Arg Leu Gly Ser Cys Leu His Gly Ser Gln Phe
 130 135 140

Pro Ser Leu
 145

<210> 435

<211> 151

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 435

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ser | Gly | Thr | Lys | Asp | Pro | Ser | Xaa | Cys | Asn | Thr | Gln | Thr | Xaa | Ala |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| His | Thr | His | Thr | Gly | Gly | Glu | Ile | Ser | Leu | Phe | Ser | Met | Ser | Phe | Phe |
| | | 20 | | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Trp | Ala | Glu | Thr | Gly | Tyr | Cys | Pro | Gly | Gln | Leu | Pro | Glu | Lys | His |
| | 35 | | | | | 40 | | | | | 45 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Arg | Glu | Leu | Arg | Ser | Ala | Arg | Pro | Ser | Ser | Leu | Ala | Pro | Gly | Phe |
| 50 | | | | | 55 | | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Gly | Pro | Arg | Thr | Ala | Asp | Arg | Gly | Trp | Ser | Trp | Arg | Leu | Xaa | Ser |
| 65 | | | | 70 | | | | | 75 | | | | | 80 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Ala | Tyr | Thr | Trp | Arg | Asn | Ala | Pro | Pro | Ser | Ser | Pro | Ser | Leu | Gln |
| | | | 85 | | | | | 90 | | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Trp | Gly | Trp | Leu | Gly | Pro | Glu | Gly | Cys | Asp | Glu | Glu | Lys | Arg | Ala |
| | 100 | | | | | 105 | | | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Val | Gly | Met | Arg | Gln | Glu | Gly | Ile | Asp | Phe | Asp | Cys | Asp | Leu | Trp |
| | 115 | | | | | 120 | | | | | | 125 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Phe | Leu | Pro | Ala | Leu | Asp | Asn | Pro | Ala | Lys | Asp | Cys | Phe | Phe | Leu |
| | 130 | | | | 135 | | | | | | 140 | | | | |

| | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|
| Ser | Leu | Ala | Arg | Arg | Gly | Pro |
| 145 | | | | | 150 | |

<210> 436

<211> 180

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (123)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 436

Ala Pro Ala Ser Pro Val Met Pro Pro Gln Thr Gln Ser Pro Gly Gln
1 5 10 15

Pro Ala Gln Pro Ala Pro Met Val Pro Leu His Gln Lys Gln Ser Arg
20 25 30

Ile Thr Pro Ile Gln Lys Pro Arg Gly Xaa Asp Pro Val Glu Ile Leu
35 40 45

Gln Glu Arg Glu Tyr Arg Leu Gln Ala Arg Ile Ala His Arg Ile Gln
50 55 60

Glu Leu Glu Asn Leu Pro Gly Ser Leu Ala Gly Asp Leu Arg Thr Lys
65 70 75 80

Ala Thr Ile Glu Leu Lys Ala Leu Arg Leu Leu Asn Phe Gln Arg Gln
85 90 95

Leu Arg Gln Glu Val Val Val Cys Met Arg Arg Asp Thr Ala Leu Glu
100 105 110

Thr Ala Leu Asn Ala Lys Ala Tyr Lys Arg Xaa Ser Ala Ser Pro Cys
115 120 125

Ala Arg Pro Ala Ser Leu Arg Ser Trp Arg Ser Ser Arg Arg Ser Ser
130 135 140

Arg Ser Ala Ser Ala Gly Arg Ser Thr Arg Asn Thr Ser Ile Ala Phe
145 150 155 160

Ser Ser Met Pro Arg Ile Ser Arg Asn Ile Thr Asp Pro Ser Gln Ala
165 170 175

Lys Ser Arg Ser
180

<210> 437

<211> 415
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (94)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (96)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (170)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 437
 Arg Lys Tyr Leu Val Pro Leu Xaa Lys Lys Leu Tyr Leu Lys Trp Ala
 1 5 10 15
 Leu Glu Glu Tyr Leu Asp Glu Phe Asp Pro Cys His Cys Arg Pro Cys
 20 25 30
 Gln Asn Gly Gly Leu Ala Thr Val Glu Gly Thr His Cys Leu Cys His
 35 40 45
 Cys Lys Pro Tyr Thr Phe Gly Ala Ala Cys Glu Gln Gly Val Leu Val
 50 55 60
 Gly Asn Gln Ala Gly Gly Val Asp Gly Gly Trp Ser Cys Trp Ser Ser
 65 70 75 80
 Trp Ser Pro Cys Val Gln Gly Lys Lys Thr Arg Ser Arg Xaa Cys Xaa
 85 90 95
 Asn Pro Pro Pro Ser Gly Gly Gly Arg Ser Cys Val Gly Glu Thr Thr
 100 105 110
 Glu Ser Thr Gln Cys Glu Asp Glu Glu Leu Glu His Leu Arg Leu Leu
 115 120 125
 Glu Pro His Cys Phe Pro Leu Ser Leu Val Pro Thr Glu Phe Cys Pro
 130 135 140

383

Ser Pro Pro Ala Leu Lys Asp Gly Phe Val Gln Asp Glu Gly Thr Met
145 150 155 160

Phe Pro Val Gly Lys Asn Val Val Tyr Xaa Cys Asn Glu Gly Tyr Ser
165 170 175

Leu Ile Gly Asn Pro Val Ala Arg Cys Gly Glu Asp Leu Arg Trp Leu
180 185 190

Val Gly Glu Met His Cys Gln Lys Ile Ala Cys Val Leu Pro Val Leu
195 200 205

Met Asp Gly Ile Gln Ser His Pro Gln Lys Pro Phe Tyr Thr Val Gly
210 215 220

Glu Lys Val Thr Val Ser Cys Ser Gly Gly Met Ser Leu Glu Gly Pro
225 230 235 240

Ser Ala Phe Leu Cys Gly Ser Ser Leu Lys Trp Ser Pro Glu Met Lys
245 250 255

Asn Ala Arg Cys Val Gln Lys Glu Asn Pro Leu Thr Gln Ala Val Pro
260 265 270

Lys Cys Gln Arg Trp Glu Lys Leu Gln Asn Ser Arg Cys Val Cys Lys
275 280 285

Met Pro Tyr Glu Cys Gly Pro Ser Leu Asp Val Cys Ala Gln Asp Glu
290 295 300

Arg Ser Lys Arg Ile Leu Pro Leu Thr Val Cys Lys Met His Val Leu
305 310 315 320

His Cys Gln Gly Arg Asn Tyr Thr Leu Thr Gly Arg Asp Ser Cys Thr
325 330 335

Leu Pro Ala Ser Ala Glu Lys Ala Cys Gly Ala Cys Pro Leu Trp Gly
340 345 350

Lys Cys Asp Ala Glu Ser Ser Lys Cys Val Cys Arg Glu Ala Ser Glu
355 360 365

Cys Glu Glu Glu Gly Phe Ser Ile Cys Val Glu Val Asn Gly Lys Glu
370 375 380

Gln Thr Met Ser Glu Cys Glu Ala Gly Ala Leu Arg Cys Arg Gly Gln
385 390 395 400

Ser Ile Ser Val Thr Ser Ile Arg Pro Cys Ala Ala Glu Thr Gln
405 410 415

<210> 438
 <211> 285
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (16)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (17)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (18)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 438
 Leu Ile Arg Leu Thr Ile Gly Lys Ala Gly Ser Leu Gln Tyr Arg Xaa
 1 5 10 15
 Xaa Xaa Phe Pro Gly Met Glu Ala Phe Leu Gly Ser Arg Ser Gly Leu
 20 25 30
 Trp Ala Gly Gly Pro Ala Pro Gly Gln Phe Tyr Arg Ile Pro Ser Thr
 35 40 45
 Pro Asp Ser Phe Met Asp Pro Ala Ser Ala Leu Tyr Arg Gly Pro Ile
 50 55 60
 Thr Arg Thr Gln Asn Pro Met Val Thr Gly Thr Ser Val Leu Gly Val
 65 70 75 80
 Lys Phe Glu Gly Gly Val Val Ile Ala Ala Asp Met Leu Gly Ser Tyr
 85 90 95
 Gly Ser Leu Ala Arg Phe Arg Asn Ile Ser Arg Ile Met Arg Val Asn
 100 105 110
 Asn Ser Thr Met Leu Gly Ala Ser Gly Asp Tyr Ala Asp Phe Gln Tyr
 115 120 125
 Leu Lys Gln Val Leu Gly Gln Met Val Ile Asp Glu Glu Leu Leu Gly
 130 135 140

385

Asp Gly His Ser Tyr Ser Pro Arg Ala Ile His Ser Trp Leu Thr Arg
145 150 155 160

Ala Met Tyr Ser Arg Arg Ser Lys Met Asn Pro Leu Trp Asn Thr Met
165 170 175

Val Ile Gly Gly Tyr Ala Asp Gly Glu Ser Phe Leu Gly Tyr Val Asp
180 185 190

Met Leu Gly Val Ala Tyr Glu Ala Pro Ser Leu Ala Thr Gly Tyr Gly
195 200 205

Ala Tyr Leu Ala Gln Pro Leu Leu Arg Glu Val Leu Glu Lys Gln Pro
210 215 220

Val Leu Ser Gln Thr Glu Ala Arg Asp Leu Val Glu Arg Cys Met Arg
225 230 235 240

Val Leu Tyr Tyr Arg Asp Ala Arg Ser Tyr Asn Arg Phe Gln Ile Ala
245 250 255

Thr Val Thr Glu Lys Gly Val Glu Ile Glu Gly Pro Leu Ser Thr Glu
260 265 270

Thr Asn Trp Asp Ile Ala His Met Ile Ser Gly Phe Glu
275 280 285

<210> 439

<211> 185

<212> PRT

<213> Homo sapiens

<400> 439

Asn Ser Ala Ala His Lys Lys Gly Lys Leu Pro Ile Val Asn Glu Asp
1 5 10 15

Asp Glu Leu Val Ala Ile Ile Ala Arg Thr Asp Leu Lys Lys Asn Arg
20 25 30

Asp Tyr Pro Leu Ala Ser Lys Asp Ala Lys Lys Gln Leu Leu Cys Gly
35 40 45

Ala Ala Ile Gly Thr His Glu Asp Asp Lys Tyr Arg Leu Asp Leu Leu
50 55 60

Ala Gln Ala Gly Val Asp Val Val Val Leu Asp Ser Ser Gln Gly Asn
65 70 75 80

Ser Ile Phe Gln Ile Asn Met Ile Lys Tyr Ile Lys Asp Lys Tyr Pro

386

| | | |
|---|-----|-----|
| 85 | 90 | 95 |
| Asn Leu Gln Val Ile Gly Gly Asn Val Val Thr Ala Ala Gln Ala Lys | | |
| 100 | 105 | 110 |
| Asn Leu Ile Asp Ala Gly Val Asp Ala Leu Arg Val Gly Met Gly Ser | | |
| 115 | 120 | 125 |
| Gly Ser Ile Cys Ile Thr Gln Glu Val Leu Ala Cys Gly Arg Pro Gln | | |
| 130 | 135 | 140 |
| Ala Thr Ala Val Tyr Lys Val Ser Glu Tyr Ala Arg Arg Phe Gly Val | | |
| 145 | 150 | 155 |
| | | 160 |
| Pro Val Ile Ala Asp Gly Gly Ile Gln Asn Val Gly His Ile Ala Lys | | |
| 165 | 170 | 175 |
| Ala Leu Ala Leu Gly Ala Pro Gln Ser | | |
| 180 | 185 | |

<210> 440
 <211> 211
 <212> PRT
 <213> Homo sapiens

<400> 440
 Leu Gln Gly Arg Ser Thr Pro Ile Trp Pro Ala Leu Ala Thr Val Thr
 1 5 10 15
 Ser Arg Thr Pro Ala Leu Gly Pro Gln Ala Gly Ile Asp Thr Asn Glu
 20 25 30
 Ile Ala Pro Leu Glu Pro Asp Ala Pro Pro Asp Ala Cys Glu Ala Ser
 35 40 45
 Phe Asp Ala Val Ser Thr Ile Arg Gly Glu Leu Phe Phe Phe Lys Ala
 50 55 60
 Gly Phe Val Trp Arg Leu Arg Gly Gly Gln Leu Gln Pro Gly Tyr Pro
 65 70 75 80
 Ala Leu Ala Ser Arg His Trp Gln Gly Leu Pro Ser Pro Val Asp Ala
 85 90 95
 Ala Phe Glu Asp Ala Gln Gly His Ile Trp Phe Phe Gln Gly Ala Gln
 100 105 110
 Tyr Trp Val Tyr Asp Gly Glu Lys Pro Val Leu Gly Pro Ala Pro Leu
 115 120 125

387

Thr Glu Leu Gly Leu Val Arg Phe Pro Val His Ala Ala Leu Val Trp
 130 135 140

Gly Pro Glu Lys Asn Lys Ile Tyr Phe Phe Arg Gly Arg Asp Tyr Trp
 145 150 155 160

Arg Phe His Pro Ser Thr Arg Arg Val Asp Ser Pro Val Pro Arg Arg
 165 170 175

Pro Leu Thr Gly Glu Gly Cys Pro Leu Arg Ser Thr Leu Pro Ser Arg
 180 185 190

Met Leu Met Ala Met Pro Thr Ser Cys Ala Ala Ala Ser Thr Gly Ser
 195 200 205

Leu Thr Leu
 210

<210> 441

<211> 80

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 441

Gly Gly Ala Gly Lys Leu Leu Ser Phe Thr His Ser Ala Pro Trp Ser
 1 5 10 15

Arg Leu Trp Ser Ser Leu Gly Lys Arg Val Thr Gly Glu Ser Gln Gly
 20 25 30

Leu Glu Lys Leu Pro Gly Thr Xaa Asp Gly Leu Ala Ala Leu Thr Gln
 35 40 45

Asp Pro Leu Pro Leu Pro Pro Pro Leu Cys Arg Asn Thr Gly Thr Pro
 50 55 60

Arg Gly Lys Met Ser Phe Ser Arg Leu Gln Phe Ser Pro Arg Lys Leu
 65 70 75 80

<210> 442
 <211> 567
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (205)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (212)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (469)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (503)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (505)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (517)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (535)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (546)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 442
 Asn Val His Leu Tyr Ile Met Tyr Tyr Met Glu Ala Lys His Ala Val
 1 5 10 15

Ser Phe Met Thr Cys Thr Gln Asn Val Ala Pro Asp Met Phe Arg Thr

389

| | | |
|---|-----|---------|
| 20 | 25 | 30 |
| Ile Pro Pro Glu Ala Asn Ile Pro Ile Pro Val Lys Ser Asp Met Val | | |
| 35 | 40 | 45 |
| Met Met His Glu His His Lys Glu Thr Glu Tyr Lys Asp Lys Ile Pro | | |
| 50 | 55 | 60 |
| Leu Leu Gln Gln Pro Lys Arg Glu Glu Glu Glu Val Leu Asp Gln Gly | | |
| 65 | 70 | 75 80 |
| Asp Phe Tyr Ser Leu Leu Ser Lys Leu Leu Gly Glu Arg Glu Asp Val | | |
| 85 | 90 | 95 |
| Val His Val His Lys Tyr Asn Pro Thr Glu Lys Ala Glu Ser Glu Ser | | |
| 100 | 105 | 110 |
| Asp Leu Val Ala Glu Ile Ala Asn Val Val Gln Lys Lys Asp Leu Gly | | |
| 115 | 120 | 125 |
| Arg Ser Asp Ala Arg Glu Gly Ala Glu His Glu Arg Gly Asn Ala Ile | | |
| 130 | 135 | 140 |
| Leu Val Arg Asp Arg Ile His Lys Phe His Arg Leu Val Ser Thr Leu | | |
| 145 | 150 | 155 160 |
| Arg Pro Pro Glu Ser Arg Val Phe Ser Leu Gln Gln Pro Pro Pro Gly | | |
| 165 | 170 | 175 |
| Glu Gly Thr Trp Glu Pro Glu His Thr Gly Asp Phe His Met Glu Glu | | |
| 180 | 185 | 190 |
| Ala Leu Asp Trp Pro Gly Val Tyr Leu Leu Pro Gly Xaa Val Ser Gly | | |
| 195 | 200 | 205 |
| Val Ala Leu Xaa Pro Lys Asn Asn Leu Val Ile Phe His Arg Gly Asp | | |
| 210 | 215 | 220 |
| His Val Trp Asp Gly Asn Ser Phe Asp Ser Lys Phe Val Tyr Gln Gln | | |
| 225 | 230 | 235 240 |
| Ile Gly Leu Gly Pro Ile Glu Glu Asp Thr Ile Leu Val Ile Asp Pro | | |
| 245 | 250 | 255 |
| Asn Asn Ala Ala Val Leu Gln Ser Ser Gly Lys Asn Leu Phe Tyr Leu | | |
| 260 | 265 | 270 |
| Pro His Gly Leu Ser Ile Asp Lys Asp Gly Asn Tyr Trp Val Thr Asp | | |
| 275 | 280 | 285 |
| Val Ala Leu His Gln Val Phe Lys Leu Asp Pro Asn Asn Lys Glu Gly | | |

390

| | | |
|---|-----|---------|
| 290 | 295 | 300 |
| Pro Val Leu Ile Leu Gly Arg Ser Met Gln Pro Gly Ser Asp Gln Asn | | |
| 305 | 310 | 315 320 |
| His Phe Cys Gln Pro Thr Asp Val Ala Val Asp Pro Gly Thr Gly Ala | | |
| | 325 | 330 335 |
| Ile Tyr Val Ser Asp Gly Tyr Cys Asn Ser Arg Ile Val Gln Phe Ser | | |
| | 340 | 345 350 |
| Pro Ser Gly Lys Phe Ile Thr Gln Trp Gly Glu Glu Ser Ser Gly Ser | | |
| | 355 | 360 365 |
| Ser Pro Leu Pro Gly Gln Phe Thr Val Pro His Ser Leu Ala Leu Val | | |
| | 370 | 375 380 |
| Pro Leu Leu Gly Gln Leu Cys Val Ala Asp Arg Glu Asn Gly Arg Ile | | |
| 385 | 390 | 395 400 |
| Gln Cys Phe Lys Thr Asp Thr Lys Glu Phe Val Arg Glu Ile Lys His | | |
| | 405 | 410 415 |
| Ser Ser Phe Gly Arg Asn Val Phe Ala Ile Ser Tyr Ile Pro Gly Leu | | |
| | 420 | 425 430 |
| Leu Phe Ala Val Asn Gly Lys Pro His Phe Gly Asp Gln Glu Pro Val | | |
| | 435 | 440 445 |
| Gln Gly Phe Val Met Asn Phe Ser Asn Gly Glu Ile Ile Asp Ile Phe | | |
| | 450 | 455 460 |
| Lys Pro Val Arg Xaa Leu Leu Asp Met Pro His Asp Ile Val Ala Ser | | |
| 465 | 470 | 475 480 |
| Glu Asp Gly Thr Val Tyr Ile Gly Arg Cys Ser Tyr Gln His Arg Val | | |
| | 485 | 490 495 |
| Gly Ser Ser Thr Leu Asp Xaa Arg Xaa Leu Gly Thr Ser Val Gln Phe | | |
| | 500 | 505 510 |
| Lys Lys Gly Leu Xaa Ile Glu Val Gln Gly Asn Pro Lys Lys Pro Glu | | |
| | 515 | 520 525 |
| Gly Ile Cys Cys Phe Pro Xaa Thr Thr Leu Arg Val Ile Pro Val Val | | |
| | 530 | 535 540 |
| Gly Xaa Trp Arg Gly His Gly Pro Asn Leu Ile Pro Val Gly Lys Asn | | |
| 545 | 550 | 555 560 |
| Pro Arg Gly Pro Leu Gly Arg | | |

391

565

<210> 443
 <211> 129
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (123)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (127)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (129)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 443
 Arg Pro Ser Cys Ser Pro Gly Ser Val Ser Ala Ala Ala Val Asn Met
 1 5 10 15
 Glu Pro Pro Asp Ala Pro Ala Gln Ala Arg Gly Ala Pro Arg Leu Leu
 20 25 30
 Leu Leu Ala Val Leu Leu Ala Ala His Pro Asp Ala Gln Ala Glu Val
 35 40 45
 Arg Leu Ser Val Pro Pro Leu Val Glu Val Met Arg Gly Lys Ser Val
 50 55 60
 Ile Leu Asp Cys Thr Pro Thr Gly Thr His Asp His Tyr Met Leu Glu
 65 70 75 80
 Trp Phe Leu Thr Asp Arg Ser Gly Ala Arg Pro Arg Leu Ala Ser Ala
 85 90 95
 Glu Met Gln Gly Ser Glu Leu Gln Val Thr Met His Asp Thr Arg Gly
 100 105 110
 Arg Ser Pro Pro Tyr Gln Leu Gly Leu Pro Xaa Gly Ala Trp Xaa Leu
 115 120 125

Xaa

392

<210> 444
<211> 131
<212> PRT
<213> Homo sapiens

<400> 444
Glu Pro Arg Val Glu Arg Glu Thr Pro Gly Gln Pro Phe Ser Ser Ser
1 5 10 15
Phe Pro Ser Pro Ser Pro Phe Pro Asn Val Ala Ser Met Trp Val Leu
20 25 30
Gly Thr Trp Glu Lys Pro Leu Leu Cys His Phe Phe Ser Leu Phe Pro
35 40 45
Ser Ser Pro Pro Thr Val Trp Leu Met Met Ser Ser Gly Val Met Val
50 55 60
Thr Thr Pro Cys Ser Leu Phe Trp Tyr Phe Pro Cys Gln Phe Pro Leu
65 70 75 80
Ser Ala Arg Leu Cys Pro Lys Ile Pro Ser Ala Ser Ser Leu His Val
85 90 95
Ala Glu Gly Pro Gly Leu Pro Gln Val Pro Cys Leu Ser Asn Lys Val
100 105 110
Glu Thr Ile Lys Pro Gly Lys Lys Lys Lys Gly Gly Arg Ser Lys Gly
115 120 125
Ser Pro Arg
130

<210> 445
<211> 405
<212> PRT
<213> Homo sapiens

<400> 445
Gly Thr Gly Leu Val Pro Ile Arg Gln Ser Thr Lys Phe Asp Ser Ser
1 5 10 15
Leu Asp Arg Lys Asp Lys Phe Ser Phe Asp Leu Gly Lys Gly Glu Val
20 25 30
Ile Lys Ala Trp Asp Ile Ala Ile Ala Thr Met Lys Val Gly Glu Val

| | | |
|---|-----|---------|
| 35 | 40 | 45 |
| Cys His Ile Thr Cys Lys Pro Glu Tyr Ala Tyr Gly Ser Ala Gly Ser | | |
| 50 | 55 | 60 |
| Pro Pro Lys Ile Pro Pro Asn Ala Thr Leu Val Phe Glu Val Glu Leu | | |
| 65 | 70 | 75 80 |
| Phe Glu Phe Lys Gly Glu Asp Leu Thr Glu Glu Glu Asp Gly Gly Ile | | |
| | 85 | 90 95 |
| Ile Arg Arg Ile Gln Thr Arg Gly Glu Gly Tyr Ala Lys Pro Asn Glu | | |
| | 100 | 105 110 |
| Gly Ala Ile Val Glu Val Ala Leu Glu Gly Tyr Tyr Lys Asp Lys Leu | | |
| | 115 | 120 125 |
| Phe Asp Gln Arg Glu Leu Arg Phe Glu Ile Gly Glu Gly Glu Asn Leu | | |
| | 130 | 135 140 |
| Asp Leu Pro Tyr Gly Leu Glu Arg Ala Ile Gln Arg Met Glu Lys Gly | | |
| 145 | 150 | 155 160 |
| Glu His Ser Ile Val Tyr Leu Lys Pro Ser Tyr Ala Phe Gly Ser Val | | |
| | 165 | 170 175 |
| Gly Lys Glu Lys Phe Gln Ile Pro Pro Asn Ala Glu Leu Lys Tyr Glu | | |
| | 180 | 185 190 |
| Leu His Leu Lys Ser Phe Glu Lys Ala Lys Glu Ser Trp Glu Met Asn | | |
| | 195 | 200 205 |
| Ser Glu Glu Lys Leu Glu Gln Ser Thr Ile Val Lys Glu Arg Gly Thr | | |
| | 210 | 215 220 |
| Val Tyr Phe Lys Glu Gly Lys Tyr Lys Gln Ala Leu Leu Gln Tyr Lys | | |
| 225 | 230 | 235 240 |
| Lys Ile Val Ser Trp Leu Glu Tyr Glu Ser Ser Phe Ser Asn Glu Glu | | |
| | 245 | 250 255 |
| Ala Gln Lys Ala Gln Ala Leu Arg Leu Ala Ser His Leu Asn Leu Ala | | |
| | 260 | 265 270 |
| Met Cys His Leu Lys Leu Gln Ala Phe Ser Ala Ala Ile Glu Ser Cys | | |
| | 275 | 280 285 |
| Asn Lys Ala Leu Glu Leu Asp Ser Asn Asn Glu Lys Gly Leu Phe Arg | | |
| | 290 | 295 300 |
| Arg Gly Glu Ala His Leu Ala Val Asn Asp Phe Glu Leu Ala Arg Ala | | |

394

305 310 315 320
 Asp Phe Gln Lys Val Leu Gln Leu Tyr Pro Asn Asn Lys Ala Ala Lys
 325 330 335
 Thr Gln Leu Ala Val Cys Gln Gln Arg Ile Arg Arg Gln Leu Ala Arg
 340 345 350
 Glu Lys Lys Leu Tyr Ala Asn Met Phe Glu Arg Leu Ala Glu Glu Glu
 355 360 365
 Asn Lys Ala Lys Ala Glu Ala Ser Ser Gly Asp His Pro Thr Asp Thr
 370 375 380
 Glu Met Lys Glu Glu Gln Lys Ser Asn Thr Ala Gly Ser Gln Ser Gln
 385 390 395 400
 Val Glu Thr Glu Ala
 405

<210> 446

<211> 232

<212> PRT

<213> Homo sapiens

<400> 446

Pro Leu Val Pro Ser Ser Gln Lys Ala Leu Leu Leu Glu Leu Lys Gly
 1 5 10 15
 Leu Gln Glu Glu Pro Val Glu Gly Phe Arg Val Thr Leu Val Asp Glu
 20 25 30
 Gly Asp Leu Tyr Asn Trp Glu Val Ala Ile Phe Gly Pro Pro Asn Thr
 35 40 45
 Tyr Tyr Glu Gly Gly Tyr Phe Lys Ala Arg Leu Lys Phe Pro Ile Asp
 50 55 60
 Tyr Pro Tyr Ser Pro Pro Ala Phe Arg Phe Leu Thr Lys Met Trp His
 65 70 75 80
 Pro Asn Ile Tyr Glu Thr Gly Asp Val Cys Ile Ser Ile Leu His Pro
 85 90 95
 Pro Val Asp Asp Pro Gln Ser Gly Glu Leu Pro Ser Glu Arg Trp Asn
 100 105 110
 Pro Thr Gln Asn Val Arg Thr Ile Leu Leu Ser Val Ile Ser Leu Leu
 115 120 125

395

Asn Glu Pro Asn Thr Phe Ser Pro Ala Asn Val Asp Ala Ser Val Met
 130 135 140

Tyr Arg Lys Trp Lys Glu Ser Lys Gly Lys Asp Arg Glu Tyr Thr Asp
 145 150 155 160

Ile Ile Arg Lys Gln Val Leu Gly Thr Arg Trp Thr Arg Val Asn Gly
 165 170 175

Val Lys Val Pro Thr Thr Leu Ala Glu Tyr Cys Val Lys Thr Lys Ala
 180 185 190

Pro Ala Pro Asp Glu Gly Ser Asp Leu Phe Tyr Asp Asp Tyr Tyr Glu
 195 200 205

Asp Gly Glu Val Glu Glu Glu^{*} Ala Asp Ser Cys Phe Gly Asp Asp Glu
 210 215 220

Asp Asp Ser Gly Thr Glu Glu Ser
 225 230

<210> 447
 <211> 356
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (12)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (53)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (191)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (263)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 447
 Cys Ser Pro Pro Pro Pro Pro Ala Ala Ala Ala Xaa Ala Ala Ala Ala

396

| | | | |
|---|-----|-----|-----|
| 1 | 5 | 10 | 15 |
| Ala Met Ala Gln Tyr Lys Gly Ala Ala Ser Glu Ala Gly Arg Ala Met | 20 | 25 | 30 |
| His Leu Met Lys Lys Arg Glu Lys Gln Arg Glu Gln Met Glu Gln Met | 35 | 40 | 45 |
| Lys Gln Arg Ile Xaa Glu Glu Asn Ile Met Lys Ser Asn Ile Asp Lys | 50 | 55 | 60 |
| Lys Phe Ser Ala His Tyr Asp Ala Val Glu Ala Glu Leu Lys Ser Ser | 65 | 70 | 75 |
| Thr Val Gly Leu Val Thr Leu Asn Asp Met Lys Ala Lys Gln Glu Ala | 85 | 90 | 95 |
| Leu Val Lys Glu Arg Glu Lys Gln Leu Ala Lys Lys Glu Gln Ser Lys | 100 | 105 | 110 |
| Glu Leu Gln Met Lys Leu Glu Lys Leu Arg Glu Lys Glu Arg Lys Lys | 115 | 120 | 125 |
| Glu Ala Lys Arg Lys Ile Ser Ser Leu Ser Phe Thr Leu Glu Glu Glu | 130 | 135 | 140 |
| Glu Glu Gly Gly Glu Glu Glu Glu Glu Ala Ala Met Tyr Glu Glu Glu | 145 | 150 | 155 |
| Met Glu Arg Glu Glu Ile Thr Thr Lys Lys Arg Lys Leu Gly Lys Asn | 165 | 170 | 175 |
| Pro Asp Val Asp Thr Ser Phe Leu Pro Asp Arg Asp Arg Glu Xaa Glu | 180 | 185 | 190 |
| Glu Asn Arg Leu Arg Glu Glu Leu Arg Gln Glu Trp Glu Ala Lys Gln | 195 | 200 | 205 |
| Glu Lys Ile Lys Ser Glu Glu Ile Glu Ile Thr Phe Ser Tyr Trp Asp | 210 | 215 | 220 |
| Gly Ser Gly His Arg Arg Thr Val Lys Met Arg Lys Gly Asn Thr Met | 225 | 230 | 235 |
| Gln Gln Phe Leu Gln Lys Ala Leu Glu Ile Leu Arg Lys Asp Phe Ser | 245 | 250 | 255 |
| Glu Leu Arg Ser Ala Gly Xaa Glu Gln Leu Met Tyr Ile Lys Glu Asp | 260 | 265 | 270 |
| Leu Ile Ile Pro His His His Ser Phe Tyr Asp Phe Ile Val Thr Lys | | | |

397

275 280 285
 Ala Arg Gly Lys Ser Gly Pro Leu Phe Asn Phe Asp Val His Asp Asp
 290 295 300
 Val Arg Leu Leu Ser Asp Ala Thr Val Glu Lys Asp Glu Ser His Ala
 305 310 315 320
 Gly Lys Val Val Leu Arg Ser Trp Tyr Glu Lys Asn Lys His Ile Phe
 325 330 335
 Pro Ala Ser Arg Trp Glu Pro Tyr Asp Pro Glu Lys Lys Trp Asp Lys
 340 345 350
 Tyr Thr Ile Arg
 355

<210> 448
 <211> 88
 <212> PRT
 <213> Homo sapiens

<400> 448
 Lys Thr His Lys Met Cys Asp Ala Phe Val Gly Thr Trp Lys Leu Val
 1 5 10 15
 Ser Ser Glu Asn Phe Asp Asp Tyr Met Lys Glu Val Gly Val Gly Phe
 20 25 30
 Ala Thr Arg Lys Val Ala Gly Met Ala Lys Pro Asn Met Ile Ile Ser
 35 40 45
 Val Asn Gly Asp Val Ile Thr Ile Lys Ser Glu Ser Thr Phe Lys Asn
 50 55 60
 Thr Glu Ile Ser Phe Ile Leu Gly Gln Glu Phe Asp Glu Ala Leu Gln
 65 70 75 80
 Met Thr Gly Lys Ser Arg Ala Pro
 85

<210> 449
 <211> 171
 <212> PRT
 <213> Homo sapiens

<220>

398

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (132)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 449

Leu Ile Leu Val Leu Met Phe Val Val Trp Met Lys Arg Arg Asp Lys
 1 5 10 15

Glu Arg Gln Ala Lys Gln Leu Leu Ile Asp Pro Glu Asp Asp Val Arg
 20 25 30

Asp Asn Ile Leu Lys Tyr Asp Glu Glu Gly Gly Gly Glu Glu Asp Gln
 35 40 45

Asp Tyr Asp Leu Ser Gln Leu Gln Gln Pro Asp Thr Val Glu Pro Asp
 50 55 60

Ala Ile Lys Pro Val Gly Ile Xaa Arg Met Asp Glu Arg Pro Ile His
 65 70 75 80

Ala Glu Pro Gln Tyr Pro Val Arg Ser Ala Ala Pro His Pro Gly Asp
 85 90 95

Ile Gly Asp Phe Ile Asn Glu Gly Leu Lys Ala Ala Asp Asn Asp Pro
 100 105 110

Thr Ala Pro Pro Tyr Asp Ser Leu Leu Val Phe Asp Tyr Glu Gly Ser
 115 120 125

Gly Ser Thr Xaa Gly Ser Leu Ser Ser Leu Asn Ser Ser Ser Gly
 130 135 140

Gly Glu Gln Asp Tyr Asp Tyr Leu Asn Asp Trp Gly Pro Arg Phe Lys
 145 150 155 160

Lys Leu Ala Asp Met Tyr Gly Gly Gly Asp Asp
 165 170

<210> 450

<211> 34

<212> PRT

<213> Homo sapiens

<400> 450

399

Lys Val Lys Ala Cys Cys Lys Asp Ile Phe Phe Leu Leu Leu Glu Gly
 1 5 10 15

Asn Thr Lys Arg Lys Ile Ser Phe Phe His Gly Ala Phe Asp Asn Phe
 20 25 30

Ser Leu

<210> 451

<211> 148

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (43)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (89)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 451

Arg Thr Leu His Pro Ala Thr Gly Pro Arg Ala Arg Pro Pro Arg Gly
 1 5 10 15

Trp Arg Arg Arg Leu Cys Ala Gln Gly Pro Ala Pro Asp Trp Asp Pro
 20 25 30

Gly Val Pro Pro Gly Leu Ala Ser Cys Gly Xaa Thr Val Trp Leu His
 35 40 45

Phe Ser Asp Pro Ser Leu Gly Arg Lys Val Lys Glu Thr Gly Pro Ala
 50 55 60

Ser Ala Phe Gly Leu Trp Phe Leu Asp Arg Val Leu Ser Pro Ser Pro
 65 70 75 80

Pro Ser Ser Pro Asn Leu Ser His Xaa Arg Pro Leu Pro Ala Ala Pro
 85 90 95

Ser Leu Leu Gly Ile Gly Ser Pro Glu Pro Pro Ser Pro Glu Pro Pro
 100 105 110

Thr Pro Leu Pro Gly Pro Cys Gly Cys Trp Ala Ser His Leu Lys Glu
 115 120 125

400

Gly Lys Val Val Gln Pro Glu Pro Val Glu Gln Cys Pro Val Trp Pro
130 135 140

Pro Lys Pro Lys
145

<210> 452
<211> 83
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (19)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (64)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (77)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (79)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 452
Asp Ser His Arg Pro Arg Ala Met Arg Ala Leu Trp Val Leu Gly Leu
1 5 10 15

Ser Cys Xaa Leu Leu Thr Phe Gly Ser Val Arg Xaa Asp Asp Glu Val
20 25 30

Asp Val Asp Gly Thr Val Glu Glu Asp Leu Gly Lys Ser Arg Glu Gly
35 40 45

Ser Arg Thr Asp Asp Glu Val Val Gln Arg Glu Glu Ala Ile Xaa
50 55 60

401

Val Gly Trp Ile Lys Cys Ile Pro Asn Lys Arg Thr Xaa Glu Xaa Lys
 65 70 75 80

Ser Arg Lys

<210> 453

<211> 240

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (234)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 453

Gly Trp Leu Pro Cys Gly Ser Ser Val Val Pro Ala Thr Pro Gly Ser
 1 5 10 15

Pro Pro Ser Arg Phe Trp Leu Leu Pro Ala Met Ala Leu Arg Val Leu
 20 25 30

Leu Leu Thr Ala Leu Thr Leu Cys His Gly Phe Asn Leu Asp Thr Glu
 35 40 45

Asn Ala Met Thr Phe Gln Glu Asn Ala Arg Gly Phe Gly Gln Ser Val
 50 55 60

Val Gln Leu Gln Gly Ser Arg Val Val Val Gly Ala Pro Gln Glu Ile
 65 70 75 80

Val Ala Ala Asn Gln Arg Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr
 85 90 95

Gly Ser Cys Glu Pro Ile His Leu Gln Val Pro Val Glu Ala Val Asn
 100 105 110

Met Ser Leu Gly Leu Ser Leu Ala Ala Thr Thr Ser Pro Pro Gln Leu
 115 120 125

Leu Ala Cys Gly Pro Thr Val His Gln Thr Cys Ser Glu Asn Thr Tyr
 130 135 140

Val Lys Gly Leu Cys Phe Leu Phe Gly Ser Asn Leu Arg Gln Gln Pro
 145 150 155 160

Gln Lys Phe Pro Glu Ala Leu Arg Gly Cys Pro Gln Glu Asp Ser Asp
 165 170 175

Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His Asp Phe
 180 185 190

Arg Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu Lys Lys
 195 200 205

Ser Lys Thr Leu Phe Ser Leu Met Gln Tyr Ser Glu Glu Phe Arg Ile
 210 215 220

His Phe Thr Ser Lys Ser Ser Arg Thr Xaa Leu Thr Gln Asp His Trp
 225 230 235 240

<210> 454
 <211> 244
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (206)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (227)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (229)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (239)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 454
 Lys Trp Cys Ser Trp Thr Leu Leu Lys Ile Trp Glu Val Thr Cys Thr
 1 5 10 15

Trp Lys Leu Pro Thr Leu Ala Lys Phe Ser Pro Tyr Leu Gly Gln Met
 20 25 30

Ile Asn Leu Arg Arg Leu Leu Leu Ser His Ile His Ala Ser Ser Tyr

403

35 40 45
 Ile Ser Pro Glu Lys Glu Glu Gln Tyr Ile Ala Gln Phe Thr Ser Gln
 50 55 60
 Phe Leu Ser Leu Gln Cys Leu Gln Leu Leu Tyr Val Asp Ser Leu Phe
 65 70 75 80
 Phe Leu Arg Gly Arg Leu Asp Gln Leu Leu Arg His Val Met Asn Pro
 85 90 95
 Leu Glu Thr Leu Ser Ile Thr Asn Cys Arg Leu Ser Glu Gly Asp Val
 100 105 110
 Met His Leu Ser Gln Ser Pro Ser Val Ser Gln Leu Ser Val Leu Ser
 115 120 125
 Leu Ser Gly Val Met Leu Thr Asp Val Ser Pro Glu Pro Leu Gln Ala
 130 135 140
 Leu Leu Glu Arg Ala Ser Ala Thr Leu Gln Asp Leu Val Phe Asp Glu
 145 150 155 160
 Cys Gly Ile Thr Asp Asp Gln Leu Leu Ala Leu Leu Pro Ser Leu Ser
 165 170 175
 His Cys Ser Gln Leu Thr Thr Leu Ser Phe Tyr Gly Asn Ser Ile Ser
 180 185 190
 Ile Ser Ala Leu Gln Ser Leu Leu Gln His Leu Ile Gly Xaa Ser Asn
 195 200 205
 Leu Thr His Val Leu Tyr Pro Val Pro Leu Glu Ser Tyr Glu Asp Ile
 210 215 220
 His Gly Xaa Leu Xaa Leu Glu Arg Leu Leu Ser Ala Cys Gln Xaa Gln
 225 230 235 240
 Gly Val Ala Val

<210> 455

<211> 195

<212> PRT

<213> Homo sapiens

<400> 455

His Glu Gly Thr Gln Ser Phe Val Phe Gln Arg Glu Glu Ile Ala Gln
 1 5 10 15

```
<210> 456
<211> 36
<212> PRT
<213> Homo sapiens
```

Leu Val Thr Leu Leu His Ala Met Gln Ala Arg Asp Lys Thr Leu Gly
1 5 10 15

Leu Ala Thr Leu Cys Ile Gly Gly Gly Gln Gly Ile Ala Met Val Ile
20 25 30

Glu Arg Leu Asn
35

<210> 457
<211> 152
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (86)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (114)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 457
Val Thr Ala Ala Ala Ser Val Arg Ala Leu Gln Val Thr Val Ala Gly
1 5 10 15
Leu Leu Leu Val Phe Phe Leu Phe Gly Ala Pro Leu Asp Ser Leu Pro
20 25 30
Ser Met Lys Ala Leu Ser Pro Val Arg Gly Cys Tyr Glu Ala Val Cys
35 40 45
Cys Leu Ser Glu Arg Ser Leu Ala Ile Ala Arg Gly Arg Gly Lys Gly
50 55 60
Pro Ala Ala Glu Glu Pro Leu Ser Leu Leu Asp Asp Met Asn His Cys
65 70 75 80
Tyr Ser Arg Leu Arg Xaa Leu Val Pro Gly Val Pro Arg Gly Thr Gln
85 90 95
Leu Ser Gln Val Glu Ile Leu Gln Arg Val Ile Asp Tyr Ile Leu Asp
100 105 110
Leu Xaa Val Val Leu Ala Glu Pro Ala Pro Gly Pro Pro Asp Gly Pro
115 120 125
His Leu Pro Ile Gln Thr Ala Glu Leu Ala Pro Glu Leu Val Ile Ser
130 135 140
Asn Asp Lys Arg Ser Phe Cys His
145 150

<210> 458
<211> 31
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (17)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (25)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (31)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 458
Leu Leu Asn Asn Phe Ile Phe Leu Glu Thr His Tyr Leu Trp Ala Cys
1 5 10 15

Xaa Thr Trp Thr Ile Trp Pro Asn Xaa Leu Asp Lys Lys Gly Xaa
20 25 30

<210> 459
<211> 157
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (28)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (72)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (124)
<223> Xaa equals any of the naturally occurring L-amino acids

407

<220>

<221> SITE

<222> (130)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 459

Asp Pro Arg Val Arg Glu Thr Thr Val Lys Ala Arg Ala Arg Ser Gln
1 5 10 15

His Ala Gly Gly Pro Glu Leu Gly Leu Ser Gln Xaa Tyr Val Thr Pro
20 25 30

Arg Arg Pro Phe Glu Lys Ser Arg Leu Asp Gln Glu Leu Lys Leu Ile
35 40 45

Gly Glu Tyr Gly Leu Arg Asn Lys Arg Glu Val Trp Arg Val Lys Phe
50 55 60

Thr Leu Ala Lys Ile Arg Lys Xaa Ala Arg Glu Leu Leu Thr Leu Asp
65 70 75 80

Glu Lys Asp Pro Arg Arg Leu Phe Glu Gly Asn Ala Leu Leu Arg Arg
85 90 95

Leu Val Arg Ile Gly Val Leu Asp Glu Gly Lys Met Lys Leu Asp Tyr
100 105 110

Ile Leu Gly Leu Lys Met Arg Ile Leu Gly Glu Xaa Ser Ala Asp Pro
115 120 125

Gly Xaa Ser Ser Trp Gly Trp Pro Ile His Pro Pro Cys Pro Val Leu
130 135 140

Ile Arg Gln Ala Thr Gln Val Arg Lys Gln Val Val Asn
145 150 155

<210> 460

<211> 136

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (119)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (130)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 460

Ile Trp Ala Pro Phe Pro His His Gln Gly Ser Gly Ser Gln Val Ser
1 5 10 15

Ser Tyr Gly Thr Gly Ala Leu Lys Ser His Ile Met Ala Ala Lys Ala
20 25 30

Val Ala Asn Thr Met Arg Thr Ser Leu Gly Pro Asn Gly Leu Asp Lys
35 40 45

Met Met Val Asp Lys Asp Gly Asp Val Thr Val Thr Asn Asp Gly Ala
50 55 60

Thr Ile Leu Ser Met Met Asp Val Asp His Gln Ile Ala Lys Leu Met
65 70 75 80

Val Glu Leu Ser Lys Ser Gln Asp Asp Glu Ile Gly Asp Gly Asp His
85 90 95

Gly Gly Gly Cys Pro Gly Arg Arg Pro Ala Gly Arg Arg Pro Ser Ser
100 105 110

Cys Trp Thr Ala Ala Phe Xaa Arg Ser Gly Ser Pro Thr Val Thr Ser
115 120 125

Arg Xaa Pro Ala Leu Ala Xaa Glu
130 135

<210> 461

<211> 390

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (375)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (382)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (383)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (386)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (387)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 461
Cys Gly Asn Trp Trp Val Pro Arg Ala Gly Xaa Asn Trp Xaa Arg Gly
1 5 10 15
Ser Arg Phe Leu Phe Val Asp Arg Cys Asp Arg His Leu Thr Met Gln
20 25 30
Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu
35 40 45
Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu
50 55 60
Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu
65 70 75 80
Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr
85 90 95
Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys
100 105 110
Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr
115 120 125

Ile Glu Asn Val Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro
130 135 140

Asp Gln Gln Arg Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg
145 150 155 160

Thr Leu Ser Asp Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val
165 170 175

Leu Arg Leu Arg Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly
180 185 190

Lys Thr Ile Thr Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val
195 200 205

Lys Ala Lys Ile Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg
210 215 220

Leu Ile Phe Ala Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp
225 230 235 240

Tyr Asn Ile Gln Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg
245 250 255

Gly Gly Met Gln Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr
260 265 270

Leu Glu Val Glu Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Lys Ile
275 280 285

Gln Asp Lys Glu Gly Ile Pro Pro Asp Gln Gln Arg Leu Ile Phe Ala
290 295 300

Gly Lys Gln Leu Glu Asp Gly Arg Thr Leu Ser Asp Tyr Asn Ile Gln
305 310 315 320

Lys Glu Ser Thr Leu His Leu Val Leu Arg Leu Arg Gly Gly Met Gln
325 330 335

Ile Phe Val Lys Thr Leu Thr Gly Lys Thr Ile Thr Leu Glu Val Glu
340 345 350

Pro Ser Asp Thr Ile Glu Asn Val Lys Ala Arg Ser Arg Gln Gly Arg
355 360 365

His Pro Pro Asp Gln Gln Xaa Leu Ile Leu Leu Gly Lys Xaa Xaa Lys
370 375 380

Trp Xaa Xaa Pro Phe Asp
385 390

411

<210> 462
 <211> 171
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (74)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (135)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (142)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (155)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 462

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Ser | Thr | Val | Arg | Ile | Pro | Gly | Ser | Thr | His | Ala | Ser | Gly | Leu | Ser |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Arg | Arg | Ala | Ser | Pro | Val | Tyr | Leu | Ala | Ser | Met | Ser | Gly | Arg | Gly | Lys |
| | | 20 | | | | | | 25 | | | | | 30 | | |
| Thr | Gly | Gly | Lys | Ala | Arg | Ala | Lys | Ala | Lys | Ser | Arg | Ser | Ser | Arg | Ala |
| | | 35 | | | | | 40 | | | | | 45 | | | |
| Gly | Leu | Gln | Phe | Pro | Val | Gly | Arg | Val | His | Arg | Leu | Leu | Arg | Lys | Gly |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| His | Tyr | Ala | Glu | Arg | Val | Gly | Ala | Gly | Xaa | Pro | Val | Tyr | Leu | Ala | Ala |
| 65 | | | | 70 | | | | | 75 | | | | | 80 | |
| Val | Leu | Glu | Tyr | Leu | Thr | Ala | Glu | Ile | Leu | Glu | Leu | Ala | Gly | Asn | Ala |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Ala | Arg | Asp | Asn | Lys | Lys | Thr | Arg | Ile | Ile | Pro | Arg | His | Leu | Gln | Leu |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Ala | Ile | Arg | Asn | Asp | Glu | Glu | Leu | Asn | Lys | Leu | Leu | Gly | Gly | Val | Thr |
| | 115 | | | | | | 120 | | | | | 125 | | | |

Ile Ala Gln Gly Arg Arg Xaa Ala Gln His Pro Gly Arg Xaa Cys Cys
 130 135 140

Pro Arg Arg Pro Ala Pro Pro Trp Gly Arg Xaa Pro Phe Gly Gly Gln
 145 150 155 160

Glu Arg Ala Thr Lys Ala Ser Gln Gly Val Leu
 165 170

<210> 463

<211> 433

<212> PRT

<213> Homo sapiens

<400> 463

Arg Val Arg Ala Pro Pro Arg Pro Pro Leu Gly Pro Ser Arg Pro Ser
 1 5 10 15

His His Val His Pro Leu Gln Leu Pro Gly Ile Arg Glu Val Thr Ile
 20 25 30

Asn Gln Ser Leu Leu Ala Pro Leu Arg Leu Asp Ala Asp Pro Ser Leu
 35 40 45

Gln Arg Val Arg Gln Glu Glu Ser Glu Gln Ile Lys Thr Leu Asn Asn
 50 55 60

Lys Phe Ala Ser Phe Ile Asp Lys Val Arg Phe Leu Glu Gln Gln Asn
 65 70 75 80

Lys Leu Leu Glu Thr Lys Trp Thr Leu Leu Gln Glu Gln Lys Ser Ala
 85 90 95

Lys Ser Ser Arg Leu Pro Asp Ile Phe Glu Ala Gln Ile Ala Gly Leu
 100 105 110

Arg Gly Gln Leu Glu Ala Leu Gln Val Asp Gly Gly Arg Leu Glu Ala
 115 120 125

Glu Leu Arg Ser Met Gln Asp Val Val Glu Asp Phe Lys Asn Lys Tyr
 130 135 140

Glu Asp Glu Ile Asn Arg Arg Thr Ala Ala Glu Asn Glu Phe Val Val
 145 150 155 160

Leu Lys Lys Asp Val Asp Ala Ala Tyr Met Ser Lys Val Glu Leu Glu
 165 170 175

Ala Lys Val Asp Ala Leu Asn Asp Glu Ile Asn Phe Leu Arg Thr Leu
180 185 190

Asn Glu Thr Glu Leu Thr Glu Leu Gln Ser Gln Ile Ser Asp Thr Ser
195 200 205

Val Val Leu Ser Met Asp Asn Ser Arg Ser Leu Asp Leu Asp Gly Ile
210 215 220

Ile Ala Glu Val Lys Ala Gln Tyr Glu Glu Met Ala Lys Cys Ser Arg
225 230 235 240

Ala Glu Ala Glu Ala Trp Tyr Gln Thr Lys Phe Glu Thr Leu Gln Ala
245 250 255

Gln Ala Gly Lys His Gly Asp Asp Leu Arg Asn Thr Arg Asn Glu Ile
260 265 270

Ser Glu Met Asn Arg Ala Ile Gln Arg Leu Gln Ala Glu Ile Asp Asn
275 280 285

Ile Lys Asn Gln Arg Ala Lys Leu Glu Ala Ala Ile Ala Glu Ala Glu
290 295 300

Glu Arg Gly Glu Leu Ala Leu Lys Asp Ala Arg Ala Lys Gln Glu Glu
305 310 315 320

Leu Glu Ala Ala Leu Gln Arg Ala Lys Gln Asp Met Ala Arg Gln Leu
325 330 335

Arg Glu Tyr Gln Glu Leu Met Ser Val Lys Leu Ala Leu Asp Ile Glu
340 345 350

Ile Ala Thr Tyr Arg Lys Leu Leu Glu Gly Glu Glu Ser Arg Leu Ala
355 360 365

Gly Asp Gly Val Gly Ala Val Asn Ile Ser Val Met Asn Ser Thr Gly
370 375 380

Gly Ser Ser Ser Gly Gly Gly Ile Gly Leu Thr Leu Gly Gly Thr Met
385 390 395 400

Gly Ser Asn Ala Leu Ser Phe Ser Ser Ser Ala Gly Pro Gly Leu Leu
405 410 415

Lys Ala Tyr Ser Ile Arg Thr Ala Ser Ala Ser Arg Arg Ser Ala Arg
420 425 430

Asp

<210> 464
<211> 121
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (64)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (110)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
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<222> (114)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (115)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (117)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 464
Gly Ser Gly Cys Val Phe Ala Ile Leu Gly Arg Arg Cys Ser Arg Pro
1 5 10 15
Trp Arg Ile Trp Pro Gly Glu Pro Leu Gln Arg Ala Pro Pro Ala Ala
20 25 30
Gly Thr Arg Trp Pro His Gly His Arg Ser Ser Pro Val Gly Thr Pro
35 40 45
Gly Xaa Ala Pro Asn Val Pro Ala Ile Trp Gln Gln Pro Leu Trp Xaa
50 55 60
Glu Tyr Ser Cys Glu Tyr Gly Ser Met Lys Phe Tyr Ala Leu Cys Gly

415

```

<400> 465
Arg Ile Pro Ala Pro Ala Ser Ser Arg His Ser Gly Gly Arg Cys Ala
 1              5              10              15
Ala Gly Pro Arg Gly Pro Pro Ala Thr Ala Ser Arg Ala Leu Arg Ala
          20              25              30
Val His Arg Pro Leu Asp Ala Ala Arg Gly Arg Thr Gly Ser Thr Ser
      35              40              45
His Leu Cys Ser Ser Ser Tyr Thr Ile Gly Cys Leu Leu Trp Phe Ser
 50              55              60
Gln Lys Ala Met
65

```

<400> 466

Ala Thr Ile Leu Glu Arg Glu Ala Glu Gln Ser Arg Leu Gly Ala Thr
1 5 10 15

Glu Arg Ala Ala Ala Ala Ala Met Asn Pro Glu Tyr Asp Tyr Leu Phe
20 25 30

Lys Leu Leu Leu Ile Gly Asp Ser Gly Val Gly Lys Ser Cys Leu Leu
35 40 45

416

Leu Arg Phe Ala Asp Asp Thr Tyr Thr Glu Ser Tyr Ile Ser Thr Ile
 50 55 60
 Gly Val Asp Phe Lys Ile Arg Thr Ile Glu Leu Asp Gly Lys Thr Ile
 65 70 75 80
 Lys Leu Gln Ile Trp Asp Thr Ala Gly Gln Glu Arg Phe Arg Thr Ile
 85 90 95
 Thr Ser Ser Tyr Tyr Arg Gly Ala His Gly Ile Ile Val Val Tyr Asp
 100 105 110
 Val Thr Asp Gln Glu Ser Tyr Ala Asn Val Lys Gln Trp Leu Gln Glu
 115 120 125
 Ile Asp Arg Tyr Ala Ser Glu Asn Val Asn Lys Leu Leu Val Gly Asn
 130 135 140
 Lys Ser Asp Leu Thr Thr Lys Lys Val Val Asp Asn Thr Thr Ala Lys
 145 150 155 160
 Glu Phe Ala Asp Ser Leu Gly Ile Pro Phe Leu Glu Thr Ser Ala Lys
 165 170 175
 Asn Ala Thr Asn Val Glu Gln Ala Phe Met Thr Met Ala Ala Glu Ile
 180 185 190
 Lys Lys Arg Met Gly Pro Gly Ala Ala Ser Gly Gly Glu Arg Pro Asn
 195 200 205
 Leu Lys Ile Asp Ser Thr Pro Val Lys Pro Ala Gly Gly Gly Cys Cys
 210 215 220

<210> 467

<211> 76

<212> PRT

<213> Homo sapiens

<400> 467

Ser Glu Ala Pro Gly Glu Ser Val Gly Thr Thr Pro Glu Ala Gln Met
 1 5 10 15
 Lys Thr Gly Pro Phe Ala Glu His Ser Asn Gln Leu Trp Asn Ile Ser
 20 25 30
 Ala Val Pro Ser Trp Ser Lys Val Asn Gln Gly Leu Ile Arg Met Tyr

417

35 40 45
 Lys Ala Glu Cys Leu Glu Lys Phe Pro Val Ile Gln His Phe Lys Phe
 50 55 60

Gly Ser Leu Leu Pro Ile His Pro Val Thr Ser Gly
 65 70 75

<210> 468

<211> 111

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (97)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 468

Ser Leu Ala Arg Thr Gly Pro Arg Ser Leu Ala Arg Pro Cys Arg Arg
 1 5 10 15

Arg Pro Ala His Arg His Pro Leu Gln Pro Cys Pro Pro Gly Xaa Cys
 20 25 30

418

Pro Arg Xaa Pro Thr Ala Asp Val Arg Arg Pro Arg His Arg Xaa Arg
 35 40 45

Xaa Glu Leu His Ala His Asn Val Thr Ser Pro Pro Ala Pro Thr Ala
 50 55 60

Trp Ala Ala Pro Ala Pro Gln His Gln Pro Gln Pro Leu Xaa Leu Val
 65 70 75 80

Pro Gly Arg Arg Val Cys Ser Arg Leu Leu Pro Arg Cys Ala Cys Gly
 85 90 95

Xaa Cys Cys Pro Gly Val Ala Leu Ala Gly Arg Ile Pro Trp Asn
 100 105 110

<210> 469

<211> 459

<212> PRT

<213> Homo sapiens

<400> 469

Pro Arg Val Arg Pro Arg Val Arg Pro Arg Val Arg Leu Ser Ser Pro
 1 5 10 15

Ser Pro Val Cys Leu Pro Pro Ala Ala Ala Thr Met Thr Thr Ser Ile
 20 25 30

Arg Gln Phe Thr Ser Ser Ser Ser Ile Lys Gly Ser Ser Gly Leu Gly
 35 40 45

Gly Gly Ser Ser Arg Thr Ser Cys Arg Leu Ser Gly Gly Leu Gly Ala
 50 55 60

Gly Ser Cys Arg Leu Gly Ser Ala Gly Gly Leu Gly Ser Thr Leu Gly
 65 70 75 80

Gly Ser Ser Tyr Ser Ser Cys Tyr Ser Phe Gly Ser Gly Gly Gly Tyr
 85 90 95

Gly Ser Ser Phe Gly Gly Val Asp Gly Leu Leu Ala Gly Gly Glu Lys
 100 105 110

Ala Thr Met Gln Asn Leu Asn Asp Arg Leu Ala Ser Tyr Leu Asp Lys
 115 120 125

Val Arg Ala Leu Glu Glu Ala Asn Thr Glu Leu Glu Val Lys Ile Arg
 130 135 140

Asp Trp Tyr Gln Arg Gln Ala Pro Gly Pro Ala Arg Asp Tyr Ser Gln
 145 150 155 160
 Tyr Tyr Arg Thr Ile Glu Glu Leu Gln Asn Lys Ile Leu Thr Ala Thr
 165 170 175
 Val Asp Asn Ala Asn Ile Leu Leu Gln Ile Asp Asn Ala Arg Leu Ala
 180 185 190
 Ala Asp Asp Phe Arg Thr Lys Phe Glu Thr Glu Gln Ala Leu Arg Leu
 195 200 205
 Ser Val Glu Ala Asp Ile Asn Gly Leu Arg Arg Val Leu Asp Glu Leu
 210 215 220
 Thr Leu Ala Arg Ala Asp Leu Glu Met Gln Ile Glu Asn Leu Lys Glu
 225 230 235 240
 Glu Leu Ala Tyr Leu Lys Lys Asn His Glu Glu Glu Met Asn Ala Leu
 245 250 255
 Arg Gly Gln Val Gly Gly Glu Ile Asn Val Glu Met Asp Ala Ala Pro
 260 265 270
 Gly Val Asp Leu Ser Arg Ile Leu Asn Glu Met Arg Asp Gln Tyr Glu
 275 280 285
 Lys Met Ala Glu Lys Asn Arg Lys Asp Ala Glu Asp Trp Phe Phe Ser
 290 295 300
 Lys Thr Glu Glu Leu Asn Arg Glu Val Ala Thr Asn Ser Glu Leu Val
 305 310 315 320
 Gln Ser Gly Lys Ser Glu Ile Ser Glu Leu Arg Arg Thr Met Gln Ala
 325 330 335
 Leu Glu Ile Glu Leu Gln Ser Gln Leu Ser Met Lys Ala Ser Leu Glu
 340 345 350
 Gly Asn Leu Ala Glu Thr Glu Asn Arg Tyr Cys Val Gln Leu Ser Gln
 355 360 365
 Ile Gln Gly Leu Ile Gly Ser Val Glu Glu Gln Leu Ala Gln Leu Arg
 370 375 380
 Cys Glu Met Glu Gln Gln Asn Gln Glu Tyr Lys Ile Leu Leu Asp Val
 385 390 395 400
 Lys Thr Arg Leu Glu Gln Glu Ile Ala Thr Tyr Arg Arg Leu Leu Glu
 405 410 415

420

Gly Glu Asp Ala His Leu Thr Gln Tyr Lys Lys Glu Pro Val Thr Thr
 420 425 430

Arg Gln Val Arg Thr Ile Val Glu Glu Val Gln Asp Gly Lys Val Ile
 435 440 445

Ser Ser Arg Glu Gln Val His Gln Thr Thr Arg
 450 455

<210> 470

<211> 158

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (158)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 470

Pro Pro Pro Pro Pro Pro Glu Leu Cys Ser Met Ala Ser Arg Arg
 1 5 10 15

Met Glu Thr Lys Pro Val Ile Thr Cys Leu Lys Thr Leu Leu Ile Ile
 20 25 30

Tyr Ser Phe Val Phe Trp Ile Thr Gly Val Ile Leu Leu Ala Val Gly
 35 40 45

Val Trp Gly Lys Leu Thr Leu Gly Thr Tyr Ile Ser Leu Ile Ala Glu
 50 55 60

Asn Ser Thr Asn Ala Pro Tyr Val Leu Ile Gly Thr Gly Thr Thr Ile
 65 70 75 80

Val Val Phe Gly Leu Phe Gly Cys Phe Ala Thr Cys Arg Gly Ser Pro
 85 90 95

Trp Met Leu Lys Leu Tyr Ala Met Phe Leu Ser Leu Val Phe Leu Ala
 100 105 110

Glu Leu Val Ala Gly Ile Ser Gly Phe Val Phe Arg His Glu Ile Lys
 115 120 125

Asp Thr Phe Leu Arg Thr Tyr Thr Asp Ala Met Gln Thr Tyr Asn Gly
 130 135 140

Asn Asp Glu Arg Ser Arg Ala Val Asp His Val Gln Arg Xaa
 145 150 155

421

<210> 471
<211> 59
<212> PRT
<213> Homo sapiens

<400> 471
Val Leu Phe Phe Tyr Glu Cys Pro Asn Leu Cys Phe Pro Leu Pro Ser
1 5 10 15
Gln Thr Val Trp Pro Val Glu Ser Val Trp Phe Val Phe Ile Ser Pro
20 25 30
Ser Phe Leu Glu Gln Gly Leu Arg Pro Cys His Ile Ser Tyr Ala Leu
35 40 45
His Pro Arg Leu Phe Trp Thr Leu Lys Val Asp
50 55

<210> 472
<211> 320
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (48)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (49)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (53)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (105)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 472
Asp Pro Asp Glu Val Phe Pro Val Cys Leu Pro Leu Thr Gly Asp Ala
1 5 10 15

Gly Glu Asp Gly Gly Lys Met Leu His Leu Pro Glu Trp Pro Glu Gln
20 25 30

Pro Pro Gly Gly Pro Ala Ala Leu Gln Val Arg Gly Ala Glu Asp Xaa
35 40 45

Xaa Leu Ser Phe Xaa Asp Cys Glu Ser Leu Gln Ala Val Phe Asp Pro
50 55 60

Ala Ser Cys Pro His Met Leu Arg Ala Pro Ala Arg Val Leu Gly Glu
65 70 75 80

Ala Val Leu Pro Phe Ser Pro Ala Leu Ala Glu Val Thr Leu Gly Ile
85 90 95

Gly Arg Gly Ala Gly Ser Ser Trp Xaa Tyr His Glu Glu Glu Ala Asp
100 105 110

Ser Thr Ala Lys Ala Met Val Thr Glu Met Cys Leu Gly Glu Glu Asp
115 120 125

Phe Gln Gln Leu Gln Ala Gln Glu Gly Val Ala Ile Thr Phe Cys Leu
130 135 140

Lys Glu Phe Arg Gly Leu Leu Ser Phe Ala Glu Ser Ala Asn Leu Asn
145 150 155 160

Leu Ser Ile His Phe Asp Ala Pro Gly Arg Pro Ala Ile Phe Thr Ile
165 170 175

Lys Asp Ser Leu Leu Asp Gly His Phe Val Leu Ala Thr Leu Ser Asp
180 185 190

Thr Asp Ser His Ser Gln Asp Leu Gly Ser Pro Glu Arg His Gln Pro
195 200 205

Val Pro Gln Leu Gln Ala His Ser Thr Pro His Pro Asp Asp Phe Ala
210 215 220

Asn Asp Asp Ile Asp Ser Tyr Met Ile Ala Met Glu Thr Thr Ile Gly
225 230 235 240

Asn Glu Gly Ser Arg Val Leu Pro Ser Ile Ser Leu Ser Pro Gly Pro
245 250 255

Gln Pro Pro Lys Ser Pro Gly Pro His Ser Glu Glu Glu Asp Glu Ala
260 265 270

Glu Pro Ser Thr Val Pro Gly Thr Pro Pro Pro Lys Lys Phe Arg Ser
275 280 285

423

Leu Phe Phe Gly Ser Ile Leu Ala Pro Val Arg Ser Pro Gln Gly Pro
 290 295 300

Ser Leu Cys Trp Arg Lys Thr Val Arg Val Lys Ala Glu Pro Arg Thr
 305 310 315 320

<210> 473

<211> 331

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (283)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (299)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (324)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 473

Pro Pro Cys Ala Val Pro Gly Pro Arg Leu Ser Pro Lys Leu Arg Thr
 1 5 10 15

Pro Ser Asn Ser Arg Glu Ser Xaa Ile Cys Val Ser Gly Arg Ala Glu
 20 25 30

Ala Leu Thr Phe Arg His Gly Ala Glu Gly Ser Asp Arg Arg Gln
 35 40 45

Arg Arg Glu Gly Val Leu Gly Pro Ala Leu Leu Cys Arg Pro Trp Glu
 50 55 60

Val Leu Gly Ala His Glu Val Pro Ser Arg Asn Ile Phe Ser Glu Gln

424

| | | | |
|---|-----|-----|-----|
| 65 | 70 | 75 | 80 |
| Thr Ile Pro Pro Ser Ala Lys Tyr Gly Gly Arg His Thr Val Thr Met | | | |
| | 85 | 90 | 95 |
| Ile Pro Gly Asp Gly Ile Gly Pro Glu Leu Met Leu His Val Lys Ser | | | |
| | 100 | 105 | 110 |
| Val Phe Arg His Ala Cys Val Pro Val Asp Phe Glu Glu Val His Val | | | |
| | 115 | 120 | 125 |
| Ser Ser Asn Ala Asp Glu Glu Asp Ile Arg Asn Ala Ile Met Ala Ile | | | |
| | 130 | 135 | 140 |
| Arg Arg Asn Arg Val Ala Leu Lys Gly Asn Ile Glu Thr Asn His Asn | | | |
| | 145 | 150 | 155 |
| | | | 160 |
| Leu Pro Pro Ser His Lys Ser Arg Asn Asn Ile Leu Arg Thr Ser Leu | | | |
| | 165 | 170 | 175 |
| Asp Leu Tyr Ala Asn Val Ile His Cys Lys Ser Leu Pro Gly Val Val | | | |
| | 180 | 185 | 190 |
| Thr Arg His Lys Asp Ile Asp Ile Leu Ile Val Arg Glu Asn Thr Glu | | | |
| | 195 | 200 | 205 |
| Gly Glu Tyr Ser Ser Leu Glu His Glu Ser Val Ala Gly Val Val Glu | | | |
| | 210 | 215 | 220 |
| Ser Leu Lys Ile Ile Thr Lys Ala Lys Ser Leu Arg Ile Ala Glu Tyr | | | |
| | 225 | 230 | 235 |
| | | | 240 |
| Ala Phe Lys Leu Ala Gln Glu Ser Gly Arg Lys Lys Val Thr Ala Val | | | |
| | 245 | 250 | 255 |
| His Lys Ala Asn Ile Met Lys Leu Gly Asp Gly Leu Phe Leu Gln Cys | | | |
| | 260 | 265 | 270 |
| Cys Arg Glu Val Ala Ala Arg Tyr Pro Gln Xaa Thr Phe Glu Asn Met | | | |
| | 275 | 280 | 285 |
| Ile Val Asp Asn Thr Thr Met Gln Leu Val Xaa Arg Pro Gln Gln Phe | | | |
| | 290 | 295 | 300 |
| Asp Val Met Val Met Pro Asn Leu Tyr Gly Asn Ile Val Lys Gln Cys | | | |
| | 305 | 310 | 315 |
| | | | 320 |
| Leu Arg Gly Xaa Gly Arg Gly Pro Lys Leu Val | | | |
| | 325 | 330 | |

425

<210> 474
<211> 30
<212> PRT
<213> Homo sapiens

<400> 474
Thr Pro Ile Ser Thr Lys Asn Thr Lys Ile Ser Gln Ala Arg Trp Arg
1 5 10 15
Ala His Val Val Pro Ala Thr Arg Glu Ala Asp Ala Glu Glu
20 25 30

<210> 475
<211> 124
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (110)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 475
Thr Gln Phe Ser Leu Ser Pro Val Glu Thr Ile Tyr Thr Ile Leu Cys
1 5 10 15
Ile Asn Val Tyr Thr Leu Pro Ile Cys Ile His Ile Tyr Ile Val Tyr
20 25 30
Ile Leu Tyr Met Tyr Arg Cys Val Tyr Val His Ile Tyr Thr His Ala
35 40 45
His Asn Lys Ile Arg Cys Ser Leu Gln Ile Gln Met Leu Ile Thr Lys
50 55 60
Pro Asp Ala Thr Gln Thr Ala Ala Glu Glu Thr Arg Leu Asp Ser Cys
65 70 75 80
Asn Arg Ser Gln Lys Ile Lys Thr Ala Thr Cys Ser Asp Phe Gly His
85 90 95
Phe Cys Met Phe Ile Lys Asn Gly Phe Val Thr Arg Lys Xaa Arg Thr
100 105 110
Ser Val Ser Glu Lys Gly Arg Trp Gly Glu Pro Ser
115 120

426

<210> 476
 <211> 64
 <212> PRT
 <213> homo sapiens

<400> 476
 Asn Gly Tyr Leu Val Phe Pro Arg Lys Asn Ser Phe Leu Leu Ile Phe
 1 5 10 15
 Gly Leu Phe Val Tyr Leu Glu Thr Asn Leu Asp Ser Leu Pro Leu Val
 20 25 30
 Asp Thr His Ser Lys Arg Thr Leu Leu Ile Lys Thr Val Glu Thr Arg
 35 40 45
 Asp Gly Gln Val Ile Asn Glu Thr Ser Gln His His Asp Asp Leu Glu
 50 55 60

<210> 477
 <211> 107
 <212> PRT
 <213> Homo sapiens

<400> 477
 Val Leu Thr Val Asp Ala Arg Asn His Gly Asp Ser Pro His Ser Pro
 1 5 10 15
 Asp Met Ser Tyr Glu Ile Met Ser Gln Asp Leu Gln Asp Leu Leu Pro
 20 25 30
 Gln Leu Gly Leu Val Pro Cys Val Val Val Gly His Ser Met Gly Gly
 35 40 45
 Lys Thr Ala Met Leu Leu Ala Leu Gln Arg Pro Glu Leu Val Glu Arg
 50 55 60
 Leu Ile Ala Val Asp Ile Ser Pro Val Glu Ser Thr Gly Val Ser His
 65 70 75 80
 Phe Ala Thr Tyr Val Ala Ala Met Arg Ala Ile Asn Ile Ala Asp Arg
 85 90 95
 Leu Ala Pro Leu Pro Cys Pro Lys Thr Gly Gly
 100 105

427

<210> 478
<211> 282
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (281)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 478
Arg Glu Leu Gly Gly Thr Leu Leu Ser Ala Ile Glu Val Glu Gly Ala
1 5 10 15
Lys Met Gln Ser Asn Lys Thr Phe Asn Leu Glu Lys Gln Asn His Thr
20 25 30
Pro Arg Lys His His Gln His His His Gln Gln Gln His His Gln Gln
35 40 45
Gln Gln Gln Gln Pro Pro Pro Pro Pro Ile Pro Ala Asn Gly Gln Gln
50 55 60
Ala Ser Ser Gln Asn Glu Gly Leu Thr Ile Asp Leu Lys Asn Phe Arg
65 70 75 80
Lys Pro Gly Glu Lys Thr Phe Thr Gln Arg Ser Arg Leu Phe Val Gly
85 90 95
Asn Leu Pro Pro Asp Ile Thr Glu Glu Glu Met Arg Lys Leu Phe Glu
100 105 110
Lys Tyr Gly Lys Ala Gly Glu Val Phe Ile His Lys Asp Lys Gly Phe
115 120 125
Gly Phe Ile Arg Leu Glu Thr Arg Thr Leu Ala Glu Ile Ala Lys Val
130 135 140
Glu Leu Asp Asn Met Pro Leu Arg Gly Lys Gln Leu Arg Val Arg Phe
145 150 155 160
Ala Cys His Ser Ala Ser Leu Thr Val Arg Asn Leu Pro Gln Tyr Val
165 170 175
Ser Asn Glu Leu Leu Glu Glu Ala Phe Ser Val Phe Gly Gln Val Glu
180 185 190
Arg Ala Val Val Ile Val Asp Asp Arg Gly Arg Pro Ser Gly Lys Gly
195 200 205

428

Ile Val Glu Phe Ser Gly Lys Pro Ala Ala Arg Lys Ala Leu Asp Arg
 210 215 220

Cys Ser Glu Gly Ser Phe Leu Leu Thr Thr Phe Pro Arg Pro Val Thr
 225 230 235 240

Val Glu Pro Met Asp Gln Leu Asp Asp Glu Glu Gly Leu Pro Glu Lys
 245 250 255

Leu Val Ile Lys Asn Gln Gln Phe His Lys Glu Arg Glu Gln Pro Pro
 260 265 270

Arg Phe Ala Gln Pro Gly Ser Phe Xaa Val
 275 280

<210> 479

<211> 289

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (206)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (215)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (218)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (285)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 479

Ala Val Pro Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Val Cys
 1 5 10 15

Gly Pro Leu Ser Ala Pro Arg Gly Ser Arg Arg Pro Thr Val Pro Gly
 20 25 30

Thr Pro Ala Cys Leu Ala Arg Pro Ala Ala Gln Gly Phe Ser Ala Ala

| | | |
|---|-----|---------|
| 35 | 40 | 45 |
| Leu Pro Val Arg Trp Thr Gly Arg Arg Ala Gly Pro Ser Arg Pro Val | | |
| 50 | 55 | 60 |
| Pro Ile Gly Thr Pro Ser Arg Ala Ala Asp Pro Ser Gln Gly Glu Met | | |
| 65 | 70 | 75 80 |
| Ser Ala Asp Ala Ala Ala Gly Ala Pro Leu Pro Arg Leu Cys Cys Leu | | |
| 85 | 90 | 95 |
| Glu Lys Gly Pro Asn Gly Tyr Gly Phe His Leu His Gly Glu Lys Gly | | |
| 100 | 105 | 110 |
| Lys Leu Gly Gln Tyr Ile Arg Leu Val Glu Pro Gly Ser Pro Ala Glu | | |
| 115 | 120 | 125 |
| Lys Ala Gly Leu Leu Ala Gly Asp Arg Leu Val Glu Val Asn Gly Glu | | |
| 130 | 135 | 140 |
| Asn Val Glu Lys Glu Thr His Gln Gln Val Val Ser Arg Ile Arg Ala | | |
| 145 | 150 | 155 160 |
| Ala Leu Asn Ala Val Arg Leu Leu Val Val Asp Pro Glu Thr Asp Glu | | |
| 165 | 170 | 175 |
| Gln Leu Gln Lys Leu Gly Val Gln Val Arg Glu Glu Leu Leu Arg Ala | | |
| 180 | 185 | 190 |
| Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro Ala Ala Ala Xaa Val Gln | | |
| 195 | 200 | 205 |
| Gly Ala Gly Asn Glu Asn Xaa Pro Arg Xaa Ala Asp Lys Ser His Pro | | |
| 210 | 215 | 220 |
| Glu Gln Arg Glu Leu Arg Pro Arg Leu Cys Thr Met Lys Lys Gly Pro | | |
| 225 | 230 | 235 240 |
| Ser Gly Tyr Gly Phe Asn Leu His Ser Asp Lys Ser Lys Pro Gly Gln | | |
| 245 | 250 | 255 |
| Phe Ile Arg Ser Val Asp Pro Asp Ser Pro Ala Glu Ala Ser Gly Leu | | |
| 260 | 265 | 270 |
| Arg Ala Gln Asp Arg Ile Val Glu Val Met Leu Leu Xaa Ser Leu Pro | | |
| 275 | 280 | 285 |
| Ile | | |

430

<210> 480

<211> 44

<212> PRT

<213> Homo sapiens

<400> 480

Gly Ser Thr His Ala Ser Gly Arg Asn Glu Gly Pro Pro Ala Lys Thr
1 5 10 15

Lys Ser Trp Val Gly Pro Thr Leu His Phe His Arg Lys Ser Glu His
20 25 30

Leu Val Gly Leu Lys Val Leu Cys Cys Phe Arg Leu
35 40

<210> 481

<211> 124

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (3)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 481

Ser Ile Xaa His Xaa Arg Lys Xaa Xaa Xaa Thr Val Arg Ser Asp Ser
1 5 10 15

431

Arg Val Asp Pro Arg Ser Asp Asp Phe Thr Pro Leu Glu Ile Leu Trp
20 25 30
Thr Phe Ser Ile Tyr Leu Glu Ser Val Ala Ile Leu Pro Gln Leu Phe
35 40 45
Met Val Ser Lys Thr Gly Glu Ala Glu Thr Ile Thr Ser His Tyr Leu
50 55 60
Phe Ala Leu Gly Val Tyr Arg Thr Leu Tyr Leu Phe Asn Trp Ile Trp
65 70 75 80
Arg Tyr His Phe Glu Gly Phe Phe Asp Leu Ile Ala Ile Val Ala Gly
85 90 95
Leu Val Gln Thr Val Leu Tyr Cys Asp Phe Phe Tyr Leu Tyr Ile Thr
100 105 110
Lys Val Leu Lys Gly Lys Lys Leu Ser Leu Pro Ala
115 120

<210> 482

<211> 131

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (122)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (124)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (127)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (131)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 482

Cys Ser Ser Arg Gly Ala His His Ser His Cys Asp Arg Leu Pro His

432

1 5 10 15
 Ser Pro Trp Pro Gly Leu Arg Glu Val Glu Leu Leu Ala Ser Val His
 20 25 30
 Thr Glu Gln Met Glu Glu Glu Leu Ala Leu Gly Pro Arg Gly Gln Gly
 35 40 45
 Gly Ala Ser Leu Ala Gly Arg Asp Gly Arg Ser Ala Gly Ala Gly Ser
 50 55 60
 Tyr Gly Ala Leu Ala Asn Ser Ala Trp Gly Gly Pro Arg Lys Val Ala
 65 70 75 80
 Ser Ala Ser Ala Ala Ala Ser Thr Leu Ser Glu Pro Pro Arg Arg Thr
 85 90 95
 Gln Glu Ser Arg Thr Arg Thr Arg Ala Leu Gly Leu Pro Thr Leu Pro
 100 105 110
 Met Glu Lys Leu Ala Ala Ser Asn Arg Xaa Pro Xaa Gly Leu Xaa Gly
 115 120 125
 Pro Gly Xaa
 130

<210> 483

<211> 221

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (168)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (174)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 483

Lys Lys Pro Pro Ile Thr His Pro Ser Thr Pro Ala Glu Glu Thr Tyr
 1 5 10 15

Asn Leu Gly Arg Gln Val Leu Pro Leu Ser Ala Val Thr Tyr Phe Gln
 20 25 30

Lys Ser Gly Pro Gly Leu Leu Pro Ala Pro Ala Thr Gln Ser Ala Ser

433

| 35 | 40 | 45 |
|---|-----|-------------|
| Val Ala Gly Thr Leu Gln Asn Ser Leu Cys Ser Gln Val Thr Lys Lys | | |
| 50 | 55 | 60 |
| Lys Arg Ala Asn Met Leu Val Leu Leu Ala Gly Ile Phe Val Val His | | |
| 65 | 70 | 75 80 |
| Ile Ala Thr Val Ile Met Leu Phe Val Ser Thr Ile Ala Asn Val Trp | | |
| | 85 | 90 95 |
| Leu Val Ser Asn Thr Val Asp Ala Ser Val Gly Leu Trp Lys Asn Cys | | |
| | 100 | 105 110 |
| Thr Asn Ile Ser Cys Ser Asp Ser Leu Ser Tyr Ala Ser Glu Asp Ala | | |
| | 115 | 120 125 |
| Leu Lys Thr Val Gln Ala Phe Met Ile Leu Ser Ile Ile Phe Cys Val | | |
| | 130 | 135 140 |
| Ile Ala Leu Leu Val Phe Val Phe Gln Leu Phe Thr Met Glu Lys Gly | | |
| | 145 | 150 155 160 |
| Asn Arg Phe Phe Leu Ser Gly Xaa Thr Thr Leu Val Cys Xaa Leu Cys | | |
| | 165 | 170 175 |
| Ile Leu Val Gly Cys Pro Ser Thr Leu Val Ile Met Arg Ile Val Met | | |
| | 180 | 185 190 |
| Glu Arg Ile Cys Thr Thr Ala Ile Pro Thr Ser Trp Ala Gly Ser Ala | | |
| | 195 | 200 205 |
| Ser Ala Ser Ala Ser Ser Ser Ala Phe Ser Ile Trp Ser | | |
| | 210 | 215 220 |

<210> 484

<211> 382

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (22)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (69)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (287)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (298)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (324)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (358)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 484
Thr Lys Leu Trp Thr Leu Val Ser Asn Pro Asp Thr Asp Ala Leu Ile
1 5 10 15
Cys Trp Ser Pro Ser Xaa Asn Ser Phe His Val Phe Asp Gln Gly Gln
20 25 30
Phe Ala Lys Glu Val Leu Pro Lys Tyr Phe Lys His Asn Asn Met Ala
35 40 45
Ser Phe Val Arg Gln Xaa Asn Met Tyr Gly Phe Arg Lys Val Val His
50 55 60
Ile Glu Gln Gly Xaa Leu Val Lys Pro Glu Arg Asp Asp Thr Glu Phe
65 70 75 80
Gln His Pro Cys Phe Leu Arg Gly Gln Glu Gln Leu Leu Glu Asn Ile
85 90 95
Lys Arg Lys Val Thr Ser Val Ser Thr Leu Lys Ser Glu Asp Ile Lys
100 105 110
Ile Arg Gln Asp Ser Val Thr Lys Leu Leu Thr Asp Val Gln Leu Met
115 120 125

435

Lys Gly Lys Gln Glu Cys Met Asp Ser Lys Leu Leu Ala Met Lys His
 130 135 140
 Glu Asn Glu Ala Leu Trp Arg Glu Val Ala Ser Leu Arg Gln Lys His
 145 150 155 160
 Ala Gln Gln Gln Lys Val Val Asn Lys Leu Ile Gln Phe Leu Ile Ser
 165 170 175
 Leu Val Gln Ser Asn Arg Ile Leu Gly Val Lys Arg Lys Ile Pro Leu
 180 185 190
 Met Leu Asn Asp Ser Gly Ser Ala His Ser Met Pro Lys Tyr Ser Arg
 195 200 205
 Gln Phe Ser Leu Glu His Val His Gly Ser Gly Pro Tyr Ser Ala Pro
 210 215 220
 Ser Pro Ala Tyr Ser Ser Ser Ser Leu Tyr Ala Pro Asp Ala Val Ala
 225 230 235 240
 Ser Ser Gly Pro Ile Ile Ser Asp Ile Thr Glu Leu Ala Pro Ala Ser
 245 250 255
 Pro Met Ala Ser Pro Gly Gly Ser Ile Asp Glu Arg Pro Leu Ser Ser
 260 265 270
 Ser Pro Leu Val Arg Val Lys Glu Glu Pro Pro Ser Pro Pro Xaa Ser
 275 280 285
 Pro Arg Val Glu Glu Ala Ser Pro Gly Xaa Pro Ser Ser Val Asp Thr
 290 295 300
 Leu Leu Ser Pro Thr Ala Leu Ile Asp Ser Ile Leu Arg Glu Ser Glu
 305 310 315 320
 Pro Ala Pro Xaa Ser Val Thr Ala Leu Thr Asp Ala Arg Gly His Thr
 325 330 335
 Asp Thr Glu Gly Arg Pro Pro Ser Pro Pro Pro Thr Ser Thr Pro Glu
 340 345 350
 Lys Cys Leu Ser Val Xaa Ala Trp Thr Arg Met Ser Ser Val Thr Thr
 355 360 365
 Trp Met Leu Trp Thr Pro Thr Trp Ile Thr Cys Arg Pro Cys
 370 375 380

<210> 485

436

<211> 416
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (399)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 485
Pro Ser Val Ala Asn Val Gly Ser His Cys Asp Leu Ser Leu Lys Ile
1 5 10 15
Pro Glu Ile Ser Ile Gln Asp Met Thr Ala Gln Val Thr Ser Pro Ser
20 25 30
Gly Lys Thr His Glu Ala Glu Ile Val Glu Gly Glu Asn His Thr Tyr
35 40 45
Cys Ile Arg Phe Val Pro Ala Glu Met Gly Thr His Thr Val Ser Val
50 55 60
Lys Tyr Lys Gly Gln His Val Pro Gly Ser Pro Phe Gln Phe Thr Val
65 70 75 80
Gly Pro Leu Gly Glu Gly Gly Ala His Lys Val Arg Ala Gly Gly Pro
85 90 95
Gly Leu Glu Arg Ala Glu Ala Gly Val Pro Ala Glu Phe Ser Ile Trp
100 105 110
Thr Arg Glu Ala Gly Ala Gly Gly Leu Ala Ile Ala Val Glu Gly Pro
115 120 125
Ser Lys Ala Glu Ile Ser Phe Glu Asp Arg Lys Asp Gly Ser Cys Gly
130 135 140
Val Ala Tyr Val Val Gln Glu Pro Gly Asp Tyr Glu Val Ser Val Lys
145 150 155 160
Phe Asn Glu Glu His Ile Pro Asp Ser Pro Phe Val Val Pro Val Ala
165 170 175
Ser Pro Ser Gly Asp Ala Arg Arg Leu Thr Val Ser Ser Leu Gln Glu
180 185 190
Ser Gly Leu Lys Val Asn Gln Pro Ala Ser Phe Ala Val Ser Leu Asn
195 200 205
Gly Ala Lys Gly Ala Ile Asp Ala Lys Val His Ser Pro Ser Gly Ala
210 215 220

437

Leu Glu Glu Cys Tyr Val Thr Glu Ile Asp Gln Asp Lys Tyr Ala Val
 225 230 235 240
 Arg Phe Ile Pro Arg Glu Asn Gly Val Tyr Leu Ile Asp Val Lys Phe
 245 250 255
 Asn Gly Thr His Ile Pro Gly Ser Pro Phe Lys Ile Arg Val Gly Glu
 260 265 270
 Pro Gly His Gly Gly Asp Pro Gly Leu Val Ser Ala Tyr Gly Ala Gly
 275 280 285
 Leu Glu Gly Gly Val Thr Gly Asn Pro Ala Glu Phe Val Val Asn Thr
 290 295 300
 Ser Asn Ala Gly Ala Gly Ala Leu Ser Val Thr Ile Asp Gly Pro Ser
 305 310 315 320
 Lys Val Lys Met Asp Cys Gln Glu Cys Pro Glu Gly Tyr Arg Val Thr
 325 330 335
 Tyr Thr Pro Met Ala Pro Gly Ser Tyr Leu Ile Ser Ile Lys Tyr Gly
 340 345 350
 Gly Pro Tyr His Ile Gly Gly Ser Pro Phe Lys Ala Lys Val Thr Gly
 355 360 365
 Pro Arg Leu Val Ser Asn His Ser Leu His Glu Thr Ser Ser Val Phe
 370 375 380
 Val Asp Ser Leu Thr Lys Ala Thr Cys Ala Pro Gln His Gly Xaa Pro
 385 390 395 400
 Gly Pro Gly Pro Ala Asp Ala Ser Lys Val Val Ala Lys Gly Trp Gly
 405 410 415

<210> 486

<211> 46

<212> PRT

<213> Homo sapiens

<400> 486

Phe Val Thr Ser Gly Lys Ile Ser Leu Tyr Val Tyr Ile Leu Thr Ile
 1 5 10 15

438

Arg Leu Asp Thr Asn Lys Ala Thr Leu Leu Thr Ala Ser Gly Glu Leu
 20 25 30

Ile Leu Phe Leu Ile Phe Phe Asn Lys Asp Ile Leu Arg Tyr
 35 40 45

<210> 487
 <211> 162
 <212> PRT
 <213> Homo sapiens

<400> 487
 Leu Gly Val Ala Leu Gly Ala Val Pro Lys Leu His Leu Gly Val Leu
 1 5 10 15

Val Ser Thr Gly Leu Arg Thr Ala Val Gly Ser Pro Arg Leu Pro Pro
 20 25 30

Thr Ala Leu Gly Ala Ala Tyr Gly Thr Ala Lys Ser Gly Thr Gly Ile
 35 40 45

Ala Ala Met Ser Val Met Arg Pro Glu Gln Ile Met Lys Ser Ile Ile
 50 55 60

Pro Val Val Met Ala Gly Ile Ile Ala Ile Tyr Gly Leu Val Val Ala
 65 70 75 80

Val Leu Ile Ala Asn Ser Leu Asn Asp Asp Ile Ser Leu Tyr Lys Ser
 85 90 95

Phe Leu Gln Leu Gly Ala Gly Leu Ser Val Gly Leu Ser Gly Leu Ala
 100 105 110

Ala Gly Phe Ala Ile Gly Ile Val Gly Asp Ala Gly Val Arg Gly Thr
 115 120 125

Ala Gln Gln Pro Arg Leu Phe Val Gly Met Ile Leu Ile Leu Ile Phe
 130 135 140

Ala Glu Val Leu Gly Leu Tyr Gly Leu Ile Val Ala Leu Ile Leu Ser
 145 150 155 160

Thr Lys

<210> 488
 <211> 114

439

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (95)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (111)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (113)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 488

Gln Ala Leu Arg Pro Gly Ser Phe Arg Gly Thr Gly Arg Lys Arg Glu
1 5 10 15

Arg Glu Arg Glu Arg Met Ser Leu Ser Asp Trp His Leu Ala Val Lys
20 25 30

Leu Ala Asp Gln Pro Leu Ala Pro Lys Ser Ile Leu Gln Leu Pro Glu
35 40 45

Ser Glu Leu Gly Glu Tyr Ser Leu Gly Gly Tyr Ser Ile Ser Phe Leu
50 55 60

Lys Gln Leu Ile Ala Gly Lys Leu Gln Glu Ser Val Pro Asp Pro Glu
65 70 75 80

Leu Ile Asp Leu Ile Tyr Cys Gly Arg Lys Leu Lys Asp Asp Xaa Thr
85 90 95

Leu Thr Ser Thr Val Phe Asn Leu Ala Pro His Pro Cys Ser Xaa Glu
100 105 110

Xaa Leu

<210> 489

<211> 149

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (121)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (142)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 489

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Thr | His | Ala | Ser | Glu | Asp | Val | Leu | Ala | Ala | Pro | Ser | Gly | Cys | Arg |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ser | Arg | Pro | Pro | Thr | Ser | Gly | Arg | Glu | Gln | Phe | Trp | Ala | Arg | Gly |
| | | | 20 | | | | | 25 | | | | | | 30 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ala | Ala | Ala | Asp | Met | Thr | Lys | Gly | Leu | Val | Leu | Gly | Ile | Tyr | Ser |
| | 35 | | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Asp | Lys | Glu | Asp | Asp | Val | Pro | Gln | Phe | Thr | Ser | Ala | Gly | Glu | Asn |
| | 50 | | | | | 55 | | | | | | 60 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Asp | Lys | Leu | Val | Ser | Gly | Lys | Leu | Arg | Glu | Ile | Leu | Asn | Ile | Ser |
| 65 | | | | | 70 | | | | 75 | | | | | 80 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Pro | Pro | Leu | Lys | Ala | Gly | Lys | Thr | Arg | Thr | Phe | Tyr | Gly | Leu | His |
| | | | 85 | | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Asp | Phe | Pro | Ser | Val | Val | Val | Val | Gly | Leu | Gly | Arg | Lys | Ala | Ala |
| | | 100 | | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Val | Asp | Asp | Gln | Glu | Asn | Trp | Xaa | Glu | Gly | Lys | Glu | Asn | Ile | Arg |
| | 115 | | | | | | 120 | | | | | | 125 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ala | Met | Gln | Arg | Gly | Ala | Gly | Arg | Phe | Gln | Asp | Leu | Xaa | Ile | Ser |
| | 130 | | | | | 135 | | | | | | 140 | | | |

| | | | | |
|-----|-----|-----|-----|-----|
| Ser | Val | Glu | Gly | Gly |
| 145 | | | | |

<210> 490

<211> 527

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (311)

<223> Xaa equals any of the naturally occurring L-amino acids

441

<400> 490

Arg Arg Arg Ser Arg Gly Leu Ile Pro Gly Arg Ala Pro Gly Arg Arg
 1 5 10 15
 Arg Pro Arg Ala His Glu Val Ala Arg Ala Pro Pro Pro Ile Ala Met
 20 25 30
 Asp Arg Met Lys Lys Ile Lys Arg Gln Leu Ser Met Thr Leu Arg Gly
 35 40 45
 Gly Arg Gly Ile Asp Lys Thr Asn Gly Ala Pro Glu Gln Ile Gly Leu
 50 55 60
 Asp Glu Ser Gly Gly Gly Gly Ser Asp Pro Gly Glu Ala Pro Thr
 65 70 75 80
 Arg Ala Ala Pro Gly Glu Leu Arg Ser Ala Arg Gly Pro Leu Ser Ser
 85 90 95
 Ala Pro Glu Ile Val His Glu Asp Leu Lys Met Gly Ser Asp Gly Glu
 100 105 110
 Ser Asp Gln Ala Ser Ala Thr Ser Ser Asp Glu Val Gln Ser Pro Val
 115 120 125
 Arg Val Arg Met Arg Asn His Pro Pro Arg Lys Ile Ser Thr Glu Asp
 130 135 140
 Ile Asn Lys Arg Leu Ser Leu Pro Ala Asp Ile Arg Leu Pro Glu Gly
 145 150 155 160
 Tyr Leu Glu Lys Leu Thr Leu Asn Ser Pro Ile Phe Asp Lys Pro Leu
 165 170 175
 Ser Arg Arg Leu Arg Arg Val Ser Leu Ser Glu Ile Gly Phe Gly Lys
 180 185 190
 Leu Glu Thr Tyr Ile Lys Leu Asp Lys Leu Gly Glu Gly Thr Tyr Ala
 195 200 205
 Thr Val Tyr Lys Gly Lys Ser Lys Leu Thr Asp Asn Leu Val Ala Leu
 210 215 220
 Lys Glu Ile Arg Leu Glu His Glu Glu Gly Ala Pro Cys Thr Ala Ile
 225 230 235 240
 Arg Glu Val Ser Leu Leu Lys Asp Leu Lys His Ala Asn Ile Val Thr
 245 250 255
 Leu His Asp Ile Ile His Thr Glu Lys Ser Leu Thr Leu Val Phe Glu

442

| 260 | 265 | 270 |
|--|-----|-----|
| Tyr Leu Asp Lys Asp Leu Lys Gln Tyr Leu Asp Asp Cys Gly Asn Ile 275 280 285 | | |
| Ile Asn Met His Asn Val Lys Leu Phe Leu Phe Gln Leu Leu Arg Gly 290 295 300 | | |
| Leu Ala Tyr Cys His Arg Xaa Lys Val Leu His Arg Asp Leu Lys Pro 305 310 315 320 | | |
| Gln Asn Leu Leu Ile Asn Glu Arg Gly Glu Leu Lys Leu Ala Asp Phe 325 330 335 | | |
| Gly Leu Ala Arg Ala Lys Ser Ile Pro Thr Lys Thr Tyr Ser Asn Glu 340 345 350 | | |
| Val Val Thr Leu Trp Tyr Arg Pro Pro Asp Ile Leu Leu Gly Ser Thr 355 360 365 | | |
| Asp Tyr Ser Thr Gln Ile Asp Met Trp Gly Val Gly Cys Ile Phe Tyr 370 375 380 | | |
| Glu Met Ala Thr Gly Arg Pro Leu Phe Pro Gly Ser Thr Val Glu Glu 385 390 395 400 | | |
| Gln Leu His Phe Ile Phe Arg Ile Leu Gly Thr Pro Thr Glu Glu Thr 405 410 415 | | |
| Trp Pro Gly Ile Leu Ser Asn Glu Glu Phe Lys Thr Tyr Asn Tyr Pro 420 425 430 | | |
| Lys Tyr Arg Ala Glu Ala Leu Leu Ser His Ala Pro Arg Leu Asp Ser 435 440 445 | | |
| Asp Gly Ala Asp Leu Leu Thr Lys Leu Leu Gln Phe Glu Gly Arg Asn 450 455 460 | | |
| Arg Ile Ser Ala Glu Asp Ala Met Lys His Pro Phe Phe Leu Ser Leu 465 470 475 480 | | |
| Gly Glu Arg Ile His Lys Leu Pro Asp Thr Thr Ser Ile Phe Ala Leu 485 490 495 | | |
| Lys Glu Ile Gln Leu Gln Lys Glu Ala Ser Leu Arg Ser Ser Ser Met 500 505 510 | | |
| Pro Asp Ser Gly Arg Pro Ala Phe Arg Val Val Asp Thr Glu Phe 515 520 525 | | |

<210> 491
<211> 125
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (125)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 491
Cys Thr Arg Ala His Pro Lys Asn Leu Val Glu Lys Gly Ile Leu Thr
1 5 10 15
Thr Glu Lys Gln Asn Phe Leu Leu Phe Asp Met Thr Thr His Pro Val
20 25 30
Thr Asn Thr Thr Glu Lys Gln Arg Leu Val Lys Lys Leu Gln Asp Ser
35 40 45
Val Leu Glu Arg Trp Val Asn Asp Pro Gln Arg Met Asp Lys Arg Thr
50 55 60
Leu Ala Leu Leu Val Leu Ala His Ser Ser Asp Val Leu Glu Asn Val
65 70 75 80
Phe Ser Ser Leu Thr Asp Asp Lys Tyr Asp Val Ala Met Asn Arg Ala
85 90 95
Lys Asp Leu Val Glu Leu Asp Pro Glu Val Glu Gly Thr Lys Pro Ser
100 105 110
Ala Thr Glu Met Ile Trp Ala Val Leu Ala Ala Phe Xaa
115 120 125

<210> 492
<211> 53
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (3)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (51)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 492

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ser | Xaa | Ser | Ile | Leu | Ala | Leu | Leu | Phe | Asn | Thr | Asp | Ala | Leu | Phe |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Arg | Val | Tyr | Glu | Ser | Leu | Ser | Asp | Asn | His | Gly | Leu | Gln | Glu | Gln |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Val | Glu | Lys | Leu | Phe | Phe | Gln | Trp | Lys | Ser | Trp | Val | Gln | Glu | Met |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | |
|-----|-----|-----|-----|-----|
| Xaa | Gly | Xaa | Leu | Lys |
| | | | 50 | |

<210> 493

<211> 82

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (60)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (67)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

445

<400> 493

Pro Gly Phe Phe Phe Gln Met Leu Val His Thr Tyr Ser Ser Met Asp
 1 5 10 15
 Arg His Asp Gly Val Pro Ser His Ser Ser Arg Leu Ser Gln Leu Gly
 20 25 30
 Ser Val Ser Gln Gly Pro Tyr Ser Ser Ala Pro Pro Leu Ser His Thr
 35 40 45
 Pro Ser Ser Asp Phe Gln Pro Pro Tyr Phe Pro Xaa Pro Tyr Gln Pro
 50 55 60
 Leu Pro Xaa Xaa Gln Ser Gln Asp Pro Tyr Ser His Val Xaa Xaa Pro
 65 70 75 80
 Tyr Pro

<210> 494

<211> 290

<212> PRT

<213> Homo sapiens

<400> 494

Tyr Lys Asp Trp Leu Thr Lys Met Ser Gly Lys His Asp Val Gly Ala
 1 5 10 15
 Tyr Met Leu Met Tyr Lys Gly Ala Asn Arg Thr Glu Thr Val Thr Ser
 20 25 30
 Phe Arg Lys Arg Glu Ser Lys Val Pro Ala Asp Leu Leu Lys Arg Ala
 35 40 45
 Phe Val Arg Met Ser Thr Ser Pro Glu Ala Phe Leu Ala Leu Arg Ser
 50 55 60
 His Phe Ala Ser Ser His Ala Leu Ile Cys Ile Ser His Trp Ile Leu
 65 70 75 80
 Gly Ile Gly Asp Arg His Leu Asn Asn Phe Met Val Ala Met Glu Thr
 85 90 95
 Gly Gly Val Ile Gly Ile Asp Phe Gly His Ala Phe Gly Ser Ala Thr
 100 105 110
 Gln Phe Leu Pro Val Pro Glu Leu Met Pro Phe Arg Leu Thr Arg Gln
 115 120 125

Phe Ile Asn Leu Met Leu Pro Met Lys Glu Thr Gly Leu Met Tyr Ser
 130 135 140
 Ile Met Val His Ala Leu Arg Ala Phe Arg Ser Asp Pro Gly Leu Leu
 145 150 155 160
 Thr Asn Thr Met Asp Val Phe Val Lys Glu Pro Ser Phe Asp Trp Lys
 165 170 175
 Asn Phe Glu Gln Lys Met Leu Lys Lys Gly Gly Ser Trp Ile Gln Glu
 180 185 190
 Ile Asn Val Ala Glu Lys Asn Trp Tyr Pro Arg Gln Lys Ile Cys Tyr
 195 200 205
 Ala Lys Arg Lys Leu Ala Gly Ala Asn Pro Ala Val Ile Thr Cys Asp
 210 215 220
 Glu Leu Leu Leu Gly His Glu Lys Ala Pro Ala Phe Arg Asp Tyr Val
 225 230 235 240
 Ala Val Ala Arg Gly Ser Lys Asp His Asn Ile Arg Ala Gln Glu Pro
 245 250 255
 Glu Ser Gly Leu Ser Glu Glu Thr Gln Val Lys Cys Leu Met Asp Gln
 260 265 270
 Ala Thr Asp Pro Asn Ile Leu Gly Arg Thr Trp Glu Gly Trp Glu Pro
 275 280 285
 Trp Met
 290

<210> 495

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (148)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 495

Cys Gln Ser His Pro Leu Pro Gly Gly Pro Ala Cys Pro Cys Leu Ala
 1 5 10 15

Cys His Ile Thr Leu Leu Phe Gly Arg Pro Trp Leu Ile Lys Glu Val

447

20 25 30
 Leu Val Val Ser Gln Ala Lys Trp Asn Leu Glu Thr Val Lys Lys Val
 35 40 45
 Gln Ile Thr Leu Asn Cys Ile Gln Glu Val His Phe Phe Pro Ile Val
 50 55 60
 Arg Gly Ser Trp Ser Leu Arg Asp Ala Arg Leu Glu Ser Asp Tyr Ile
 65 70 75 80
 Ile Ile Gln Asn Gly Asn Ser Gln Gly Asn Ala Phe Phe His Phe Ile
 85 90 95
 Arg Phe Phe Tyr Pro His Cys Thr Pro Ser Pro Ser Pro Leu Pro Ile
 100 105 110
 Trp Met Ala Ser Gln Lys Leu Gly Pro Ser Pro Pro Cys Leu Gly Gly
 115 120 125
 Gly Gln Ser Pro Leu Thr Ala Glu Ala Ala Leu Leu Ser Ser Ala Val
 130 135 140
 Leu Pro Leu Xaa Lys Cys Leu Gln Arg Val Met Ser
 145 150 155

<210> 496

<211> 251

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 496

Glu Glu Leu Leu Arg Ala Gln Glu Ala Pro Gly Gln Ala Glu Pro Pro
 1 5 10 15
 Ala Ala Ala Glu Val Gln Gly Ala Gly Asn Glu Asn Glu Pro Arg Glu
 20 25 30
 Ala Asp Lys Ser His Pro Glu Gln Arg Xaa Leu Arg Pro Arg Leu Cys
 35 40 45
 Thr Met Lys Lys Gly Pro Ser Gly Tyr Gly Phe Asn Leu His Ser Asp
 50 55 60

Lys Ser Lys Pro Gly Gln Phe Ile Arg Ser Val Asp Pro Asp Ser Pro
 65 70 75 80
 Ala Glu Ala Ser Gly Leu Arg Ala Gln Asp Arg Ile Val Glu Val Asn
 85 90 95
 Gly Val Cys Met Glu Gly Lys Gln His Gly Asp Val Val Ser Ala Ile
 100 105 110
 Arg Ala Gly Gly Asp Glu Thr Lys Leu Leu Val Val Asp Arg Glu Thr
 115 120 125
 Asp Glu Phe Phe Lys Lys Cys Arg Val Ile Pro Ser Gln Glu His Leu
 130 135 140
 Asn Gly Pro Leu Pro Val Pro Phe Thr Asn Gly Glu Ile Gln Lys Glu
 145 150 155 160
 Asn Ser Arg Glu Ala Leu Ala Glu Ala Ala Leu Glu Ser Pro Arg Pro
 165 170 175
 Ala Leu Val Arg Ser Ala Ser Ser Asp Thr Ser Glu Glu Leu Asn Ser
 180 185 190
 Gln Asp Ser Pro Pro Lys Gln Asp Ser Thr Ala Pro Ser Ser Thr Ser
 195 200 205
 Ser Ser Asp Pro Ile Leu Asp Phe Asn Ile Ser Leu Ala Met Ala Lys
 210 215 220
 Glu Arg Ala His Gln Lys Arg Ser Ser Lys Arg Ala Pro Gln Met Asp
 225 230 235 240
 Trp Ser Lys Lys Asn Glu Leu Phe Ser Asn Leu
 245 250

<210> 497

<211> 48

<212> PRT

<213> Homo sapiens

<400> 497

Asn Gly Ala Glu Ala Val Ser Thr Glu Ala Lys Met Thr Ala Phe Pro
 1 5 10 15
 Asp Trp Pro Trp Leu Phe His Thr Leu Cys Asp Pro Cys Pro Met Thr
 20 25 30
 Leu Trp Leu Thr Leu Pro Glu Ala Met Thr Thr Ala Ala Phe Cys His

35

40

45

<210> 498

<211> 373

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (337)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (372)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 498

Gly Thr Arg Gly Ser Arg Ala Ser Gly Val Cys Ala Arg Gly Cys Leu
1 5 10 15

Asp Ser Ala Gly Pro Trp Thr Met Ser Arg Ala Leu Arg Pro Pro Leu
20 25 30

Pro Pro Leu Cys Phe Phe Leu Leu Leu Ala Ala Gly Ala Arg
35 40 45

Ala Gly Gly Tyr Glu Thr Cys Pro Thr Val Gln Pro Asn Met Leu Asn
50 55 60

Val His Leu Leu Pro His Thr His Asp Asp Val Gly Trp Leu Lys Thr
65 70 75 80

Val Asp Gln Tyr Phe Tyr Gly Ile Lys Asn Asp Ile Gln His Ala Gly
85 90 95

Val Gln Tyr Ile Leu Asp Ser Val Ile Ser Ala Leu Leu Ala Asp Pro
100 105 110

Thr Arg Arg Phe Ile Tyr Val Glu Ile Ala Phe Phe Ser Arg Trp Trp
115 120 125

His Gln Gln Thr Asn Ala Thr Gln Glu Val Val Arg Asp Leu Val Arg
130 135 140

Gln Gly Arg Leu Glu Phe Ala Asn Gly Gly Trp Val Met Asn Asp Glu

450

145 150 155 160
 Ala Ala Thr His Tyr Gly Ala Ile Val Asp Gln Met Thr Leu Gly Leu
 165 170 175
 Arg Phe Leu Glu Asp Thr Phe Gly Asn Asp Gly Arg Pro Arg Val Ala
 180 185 190
 Trp His Ile Asp Pro Phe Gly His Ser Arg Glu Gln Ala Ser Leu Phe
 195 200 205
 Ala Gln Met Gly Phe Asp Gly Phe Phe Phe Gly Arg Leu Asp Tyr Gln
 210 215 220
 Asp Lys Trp Val Arg Met Gln Lys Leu Glu Met Glu Gln Val Trp Arg
 225 230 235 240
 Ala Ser Thr Ser Leu Lys Pro Pro Thr Ala Asp Leu Phe Thr Gly Val
 245 250 255
 Leu Pro Asn Gly Tyr Asn Pro Pro Arg Asn Leu Cys Trp Asp Val Leu
 260 265 270
 Cys Val Asp Gln Pro Leu Val Glu Asp Pro Arg Ser Pro Glu Tyr Asn
 275 280 285
 Ala Lys Glu Leu Val Asp Tyr Phe Leu Asn Val Ala Thr Ala Gln Gly
 290 295 300
 Arg Tyr Tyr Arg Thr Asn His Thr Val Met Thr Met Gly Ser Asp Phe
 305 310 315 320
 Gln Tyr Glu Asn Ala Asn Met Trp Phe Lys Asn Leu Asp Lys Leu Ile
 325 330 335
 Xaa Leu Val Asn Ala Gln Gly Lys Arg Lys Gln Cys Pro Cys Ser Leu
 340 345 350
 Leu His Pro Arg Leu Leu Pro Leu Gly Ala Glu Gln Gly Gln Pro His
 355 360 365
 Leu Val Ser Xaa Thr
 370

<210> 499

<211> 238

<212> PRT

<213> Homo sapiens

451

<400> 499

Ala Leu Pro Gly Pro Asp Trp His Gly Ala Gly Ala Ala Asp Arg Gly
1 5 10 15

Pro Ala Ala Pro Pro Arg Pro Gly Pro Cys Ala Tyr Ala Ala His Gly
20 25 30

Arg Gly Ala Leu Ala Glu Ala Ala Arg Arg Cys Leu His Asp Ile Ala
35 40 45

Leu Ala His Arg Ala Ala Thr Ala Ala Arg Pro Pro Ala Pro Pro Pro
50 55 60

Ala Pro Gln Pro Pro Ser Pro Thr Pro Ser Pro Pro Arg Pro Thr Leu
65 70 75 80

Ala Arg Glu Asp Asn Glu Glu Asp Glu Asp Glu Pro Thr Glu Thr Glu
85 90 95

Thr Ser Gly Glu Gln Leu Gly Ile Ser Asp Asn Gly Gly Leu Phe Val
100 105 110

Met Asp Glu Asp Ala Thr Leu Gln Asp Leu Pro Pro Phe Cys Glu Ser
115 120 125

Asp Pro Glu Ser Thr Asp Asp Gly Ser Leu Ser Glu Glu Thr Pro Ala
130 135 140

Gly Pro Pro Thr Cys Ser Val Pro Pro Ala Ser Ala Leu Pro Thr Gln
145 150 155 160

Gln Tyr Ala Lys Ser Leu Pro Val Ser Val Pro Val Trp Gly Phe Lys
165 170 175

Glu Lys Arg Thr Glu Ala Arg Ser Ser Asp Glu Glu Asn Gly Pro Pro
180 185 190

Ser Ser Pro Asp Leu Asp Arg Ile Ala Ala Ser Met Arg Ala Leu Val
195 200 205

Leu Arg Glu Ala Glu Asp Thr Gln Val Phe Gly Asp Leu Pro Arg Pro
210 215 220

Arg Leu Asn Thr Ser Asp Phe Gln Lys Leu Lys Arg Lys Tyr
225 230 235

<210> 500

<211> 198

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (94)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (156)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 500

Asn Ser Ala Glu Leu Ser Pro Gly Leu Cys Ser Pro Thr Pro Thr Glu
1 5 10 15

Ala Arg Ala Gly Asp Ala Gly Pro Ala Ala Arg Ser Arg Lys Gln Asn
20 25 30

Pro Gln Ser Pro Pro Cys Cys Cys Val Asp Asp Thr Trp Ala Gln Ala
35 40 45

Glu Val Gly Pro Val Thr Ser Cys Thr Gly Phe Val Glu Gly Ser Ser
50 55 60

Arg Thr Gly Gly Met Gly Ser Ala Cys Ile Lys Val Thr Lys Tyr Phe
65 70 75 80

Leu Phe Leu Phe Asn Leu Ile Phe Phe Ile Leu Gly Ala Xaa Ile Leu
85 90 95

Gly Phe Gly Val Trp Ile Leu Ala Asp Lys Ser Ser Phe Ile Ser Val
100 105 110

Leu Gln Thr Ser Ser Ser Ser Leu Arg Met Gly Ala Tyr Val Phe Ile
115 120 125

Gly Val Gly Ala Val Thr Met Leu Met Gly Phe Leu Gly Cys Ile Gly
130 135 140

Ala Val Asn Glu Val Arg Cys Leu Leu Gly Leu Xaa Phe Ala Phe Leu
145 150 155 160

Leu Leu Ile Leu Ile Ala Gln Val Thr Ala Gly Ala Leu Phe Tyr Phe
165 170 175

Asn Met Gly Lys Val Ser Pro Ser Leu Pro Pro Ser Ser Leu Gly Trp
180 185 190

Thr Asn His Gly Gly Asp
195

<210> 501

<211> 169

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (165)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 501

Ser Ser Ala Ser Thr Asn Met Ser Arg Gly Ser Ser Ala Gly Phe Asp
1 5 10 15

Arg His Ile Thr Ile Phe Ser Pro Glu Gly Arg Leu Tyr Gln Val Glu
20 25 30

Tyr Ala Phe Lys Ala Ile Asn Gln Gly Gly Leu Thr Ser Val Ala Val
35 40 45

Arg Gly Lys Asp Cys Ala Val Ile Val Thr Gln Lys Lys Val Pro Asp
50 55 60

Lys Leu Leu Asp Ser Ser Thr Val Thr His Leu Phe Lys Ile Thr Glu
65 70 75 80

Asn Ile Gly Cys Val Met Thr Gly Met Thr Ala Asp Ser Arg Ser Gln
85 90 95

Val Gln Arg Ala Arg Tyr Glu Ala Ala Asn Trp Lys Tyr Lys Tyr Gly
100 105 110

Tyr Glu Ile Pro Val Asp Met Leu Cys Lys Arg Ile Ala Asp Ile Ser
115 120 125

Gln Val Tyr Thr Gln Asn Ala Glu Met Arg Pro Leu Gly Cys Cys Met
130 135 140

Ile Leu Ile Gly Ile Asp Glu Glu Gln Gly Pro Gln Val Tyr Lys Cys
145 150 155 160

Asp Pro Ala Gly Xaa Tyr Cys Gly Val
165

<210> 502

<211> 507

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (361)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (461)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 502

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Arg | Gln | Leu | Cys | Arg | Pro | Ala | Glu | Xaa | Asp | Ser | Val | Met | Ala | Glu |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gln | Val | Ala | Leu | Ser | Arg | Thr | Gln | Val | Cys | Gly | Ile | Leu | Arg | Glu | Glu |
| | | | 20 | | | | | | 25 | | | | | 30 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Phe | Gln | Gly | Asp | Ala | Phe | His | Gln | Ser | Asp | Thr | His | Ile | Phe | Ile |
| | | 35 | | | | | 40 | | | | | | 45 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Met | Gly | Ala | Ser | Gly | Asp | Leu | Ala | Lys | Lys | Lys | Ile | Tyr | Pro | Thr |
| | 50 | | | | | 55 | | | | | | 60 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Trp | Trp | Leu | Phe | Arg | Asp | Gly | Leu | Leu | Pro | Glu | Asn | Thr | Phe | Ile |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Gly | Tyr | Ala | Arg | Ser | Arg | Leu | Thr | Val | Ala | Asp | Ile | Arg | Lys | Gln |
| | | | | 85 | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Glu | Pro | Phe | Phe | Lys | Ala | Thr | Pro | Glu | Glu | Lys | Leu | Lys | Leu | Glu |
| | | 100 | | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Phe | Phe | Ala | Arg | Asn | Ser | Tyr | Val | Ala | Gly | Gln | Tyr | Asp | Asp | Ala |
| | 115 | | | | | | 120 | | | | | 125 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Ser | Tyr | Gln | Arg | Leu | Asn | Ser | His | Met | Asn | Ala | Leu | His | Leu | Gly |
| | 130 | | | | | 135 | | | | | 140 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Gln | Ala | Asn | Arg | Leu | Phe | Tyr | Leu | Ala | Leu | Pro | Pro | Thr | Val | Tyr |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Ala | Val | Thr | Lys | Asn | Ile | His | Glu | Ser | Cys | Met | Ser | Gln | Ile | Gly |
| | | | | 165 | | | | 170 | | | | | | 175 | |

455

Trp Asn Arg Ile Ile Val Glu Lys Pro Phe Gly Arg Asp Leu Gln Ser
 180 185 190
 Ser Asp Arg Leu Ser Asn His Ile Ser Ser Leu Phe Arg Glu Asp Gln
 195 200 205
 Ile Tyr Arg Ile Asp His Tyr Leu Gly Lys Glu Met Val Gln Asn Leu
 210 215 220
 Met Val Leu Arg Phe Ala Asn Arg Ile Phe Gly Pro Ile Trp Asn Arg
 225 230 235 240
 Asp Asn Ile Ala Cys Val Ile Leu Thr Phe Lys Glu Pro Phe Gly Thr
 245 250 255
 Glu Gly Arg Gly Gly Tyr Phe Asp Glu Phe Gly Ile Ile Arg Asp Val
 260 265 270
 Met Gln Asn His Leu Leu Gln Met Leu Cys Leu Val Ala Met Glu Lys
 275 280 285
 Pro Ala Ser Thr Asn Ser Asp Asp Val Arg Asp Glu Lys Val Lys Val
 290 295 300
 Leu Lys Cys Ile Ser Glu Val Gln Ala Asn Asn Val Val Leu Gly Gln
 305 310 315 320
 Tyr Val Gly Asn Pro Asp Gly Glu Gly Glu Ala Thr Lys Gly Tyr Leu
 325 330 335
 Asp Asp Pro Thr Val Pro Arg Gly Ser Thr Thr Ala Thr Phe Ala Ala
 340 345 350
 Val Val Leu Tyr Val Glu Asn Glu Xaa Trp Asp Gly Val Pro Phe Ile
 355 360 365
 Leu Arg Cys Gly Lys Ala Leu Asn Glu Arg Lys Ala Glu Val Arg Leu
 370 375 380
 Gln Phe His Asp Val Ala Gly Asp Ile Phe His Gln Gln Cys Lys Arg
 385 390 395 400
 Asn Glu Leu Val Ile Arg Val Gln Pro Asn Glu Ala Val Tyr Thr Lys
 405 410 415
 Met Met Thr Lys Lys Pro Gly Met Phe Phe Asn Pro Glu Glu Ser Glu
 420 425 430
 Leu Asp Leu Thr Tyr Gly Asn Arg Tyr Lys Asn Val Lys Leu Pro Asp
 435 440 445

456

Ala Tyr Glu Arg Leu Ile Leu Asp Val Phe Cys Gly Xaa Gln Met His
 450 455 460

Phe Val Arg Arg Thr Ser Ser Val Arg Pro Gly Val Phe Ser Pro His
 465 470 475 480

Cys Cys Thr Arg Leu Ser Trp Arg Ser Pro Ser Pro Ser Pro Ile Phe
 485 490 495

Met Ala Ala Glu Ala Pro Arg Arg Gln Thr Ser
 500 505

<210> 503

<211> 260

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (69)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 503

Gly Pro Glu Val Leu Pro Glu Pro Arg Val Pro Arg Glu Ala Leu Ala
 1 5 10 15

Phe Ile Ile Arg Ser Phe Gly Gly Glu Val Ser Trp Asp Lys Ser Leu
 20 25 30

Cys Ile Gly Ala Thr Tyr Asp Val Thr Asp Ser Arg Ile Thr His Gln
 35 40 45

Ile Val Asp Arg Pro Gly Gln Gln Thr Ser Val Ile Gly Arg Cys Tyr
 50 55 60

Val Gln Pro Gln Xaa Val Phe Asp Ser Val Asn Ala Arg Leu Leu Leu
 65 70 75 80

Pro Val Ala Glu Tyr Phe Ser Gly Val Gln Leu Pro Pro His Leu Ser
 85 90 95

Pro Phe Val Thr Glu Lys Glu Gly Asp Tyr Val Pro Pro Glu Lys Leu
 100 105 110

Lys Leu Leu Ala Leu Gln Arg Gly Glu Asp Pro Gly Asn Leu Asn Glu
 115 120 125

Ser Glu Glu Glu Glu Glu Asp Asp Asn Asn Glu Gly Asp Gly Asp

130 135 140
 Glu Glu Gly Glu Asn Glu Glu Glu Glu Asp Ala Glu Ala Gly Ser
 145 150 155 160
 Glu Lys Glu Glu Glu Ala Arg Leu Ala Ala Leu Glu Glu Gln Arg Met
 165 170 175
 Glu Gly Lys Lys Pro Arg Val Met Ala Gly Thr Leu Lys Leu Glu Asp
 180 185 190
 Lys Gln Arg Leu Ala Gln Glu Glu Glu Ser Glu Ala Lys Arg Leu Ala
 195 200 205
 Ile Met Met Met Lys Lys Arg Glu Lys Tyr Leu Tyr Gln Lys Ile Met
 210 215 220
 Phe Gly Lys Arg Arg Lys Ile Arg Glu Ala Asn Lys Leu Ala Glu Lys
 225 230 235 240
 Arg Lys Ala His Asp Glu Ala Val Arg Ser Glu Lys Lys Ala Lys Lys
 245 250 255
 Ala Arg Pro Glu
 260

<210> 504

<211> 424

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (292)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (342)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 504

Leu Leu Gln Arg Cys Tyr Ala Phe Pro Gly His Arg Leu Ala His Ser
 1 5 10 15

Gly Ser Asp Leu Ser Leu Leu Val Pro Glu Ile Glu Asp Met Tyr Ser
 20 25 30

Ser Pro Tyr Leu Arg Pro Ser Glu Ser Pro Ile Thr Val Glu Val Asn

458

| | | |
|---|-----|---------|
| 35 | 40 | 45 |
| Cys Thr Asn Pro Gly Thr Arg Tyr Cys Trp Met Ser Thr Gly Leu Tyr | | |
| 50 | 55 | 60 |
| Ile Pro Gly Arg Gln Ile Ile Glu Val Ser Leu Pro Glu Ala Ala Ala | | |
| 65 | 70 | 75 80 |
| Ser Ala Asp Leu Lys Ile Gln Ile Gly Cys His Thr Asp Asp Leu Thr | | |
| 85 | 90 | 95 |
| Arg Ala Ser Lys Leu Phe Arg Gly Pro Leu Val Ile Asn Arg Cys Cys | | |
| 100 | 105 | 110 |
| Leu Asp Lys Pro Thr Lys Ser Ile Thr Cys Leu Trp Gly Gly Leu Leu | | |
| 115 | 120 | 125 |
| Tyr Ile Ile Val Pro Gln Asn Ser Lys Leu Gly Ser Val Pro Val Thr | | |
| 130 | 135 | 140 |
| Val Lys Gly Ala Val His Ala Pro Tyr Tyr Lys Leu Gly Glu Thr Thr | | |
| 145 | 150 | 155 160 |
| Leu Glu Glu Trp Lys Arg Arg Ile Gln Glu Asn Pro Gly Pro Trp Gly | | |
| 165 | 170 | 175 |
| Glu Leu Ala Thr Asp Asn Ile Ile Leu Thr Val Pro Thr Ala Asn Leu | | |
| 180 | 185 | 190 |
| Arg Thr Leu Glu Asn Pro Glu Pro Leu Leu Arg Leu Trp Asp Glu Val | | |
| 195 | 200 | 205 |
| Met Gln Ala Val Ala Arg Leu Gly Ala Glu Pro Phe Pro Leu Arg Leu | | |
| 210 | 215 | 220 |
| Pro Gln Arg Ile Val Ala Asp Val Gln Ile Ser Val Gly Trp Met His | | |
| 225 | 230 | 235 240 |
| Ala Gly Tyr Pro Ile Met Cys His Leu Glu Ser Val Gln Glu Leu Ile | | |
| 245 | 250 | 255 |
| Asn Glu Lys Leu Ile Arg Thr Lys Gly Leu Trp Gly Pro Val His Glu | | |
| 260 | 265 | 270 |
| Leu Gly Arg Asn Gln Gln Arg Gln Glu Trp Glu Phe Pro Pro His Thr | | |
| 275 | 280 | 285 |
| Thr Glu Ala Xaa Cys Asn Leu Trp Cys Val Tyr Val His Glu Thr Val | | |
| 290 | 295 | 300 |
| Leu Gly Ile Pro Arg Ser Arg Ala Asn Ile Ala Leu Trp Pro Pro Val | | |

459

305 310 315 320
Arg Glu Lys Arg Val Arg Ile Tyr Leu Ser Lys Gly Pro Asn Val Lys
 325 330 335
Asn Trp Asn Ala Trp Xaa Ala Leu Glu Thr Tyr Leu Gln Leu Gln Glu
 340 345 350
Ala Phe Gly Trp Glu Pro Phe Ile Arg Leu Phe Thr Glu Tyr Arg Asn
 355 360 365
Gln Thr Asn Leu Pro Thr Glu Asn Val Asp Lys Met Asn Leu Trp Val
 370 375 380
Lys Met Phe Ser His Gln Val Gln Lys Asn Leu Ala Pro Phe Phe Glu
385 390 395 400
Ala Trp Ala Gly Pro Ser Arg Arg Lys Trp Leu Pro Ala Trp Pro Ile
 405 410 415
Cys Leu Asn Gly Arg Lys Ile Leu
 420

<210> 505

<211> 70

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (49)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (66)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (70)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 505

Leu His Gln Ser Leu Leu His Leu Glu Lys Thr Asn Glu Arg Lys Ser
1 5 10 15
Ile Phe Leu Ile His Tyr Pro Asn Asn Asn Arg Thr Pro Tyr Arg Asn
20 25 30
Tyr Tyr His Tyr Val Ser Lys His Tyr Ile Pro Ile Thr Tyr Pro Thr
35 40 45
Xaa Ser Ile Ile Asp Xaa Ile Ser Ile Pro Thr Met Ile Ser Ala Leu
50 55 60
Asn Xaa Gln Asn Lys Xaa
65 70

<210> 506
<211> 434
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (69)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (135)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (363)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 506
Ser Thr His Ala Ser Ala His Ala Ser Val Ser Thr Ala Ala Ala Ala
1 5 10 15
Ala Leu Ala Ala Ala Val Lys Ala Lys His Leu Ala Ala Val Glu
20 25 30
Glu Arg Lys Ile Lys Ser Leu Val Ala Leu Leu Val Glu Thr Gln Met
35 40 45
Lys Lys Leu Glu Ile Lys Leu Arg His Phe Glu Glu Leu Glu Thr Ile
50 55 60
Met Asp Arg Glu Xaa Glu Ala Leu Glu Tyr Gln Arg Gln Gln Leu Leu

461

| | | | |
|---|-----|-----|-----|
| 65 | 70 | 75 | 80 |
| Ala Asp Arg Gln Ala Phe His Met Glu Gln Leu Lys Tyr Ala Glu Met | 85 | 90 | 95 |
| Arg Ala Arg Gln Gln His Phe Gln Gln Met His Gln Gln Gln Gln Gln | 100 | 105 | 110 |
| Pro Pro Pro Ala Leu Pro Pro Gly Ser Gln Pro Ile Pro Pro Thr Gly | 115 | 120 | 125 |
| Ala Ala Gly Pro Pro Ala Xaa His Gly Leu Ala Val Ala Pro Ala Ser | 130 | 135 | 140 |
| Val Val Pro Ala Pro Ala Gly Ser Gly Ala Pro Pro Gly Ser Leu Gly | 145 | 150 | 155 |
| Pro Ser Glu Gln Ile Gly Gln Ala Gly Ser Thr Ala Gly Pro Gln Gln | 165 | 170 | 175 |
| Gln Gln Pro Ala Gly Ala Pro Gln Pro Gly Ala Val Pro Pro Gly Val | 180 | 185 | 190 |
| Pro Pro Pro Gly Pro His Gly Pro Ser Pro Phe Pro Asn Gln Gln Thr | 195 | 200 | 205 |
| Pro Pro Ser Met Met Pro Gly Ala Val Pro Gly Ser Gly His Pro Gly | 210 | 215 | 220 |
| Val Ala Gly Asn Ala Pro Leu Gly Leu Pro Phe Gly Met Pro Pro Pro | 225 | 230 | 235 |
| Pro Pro Pro Pro Ala Pro Ser Ile Ile Pro Phe Gly Ser Leu Ala Asp | 245 | 250 | 255 |
| Ser Ile Ser Ile Asn Leu Pro Ala Pro Pro Asn Leu His Gly His His | 260 | 265 | 270 |
| His His Leu Pro Phe Ala Pro Gly Thr Leu Pro Pro Pro Asn Leu Pro | 275 | 280 | 285 |
| Val Ser Met Ala Asn Pro Leu His Pro Asn Leu Pro Ala Thr Thr Thr | 290 | 295 | 300 |
| Met Pro Ser Ser Leu Pro Leu Gly Pro Gly Leu Gly Ser Ala Ala Ala | 305 | 310 | 315 |
| Gln Ser Pro Ala Ile Val Ala Ala Val Gln Gly Asn Leu Leu Pro Ser | 325 | 330 | 335 |
| Ala Ser Pro Leu Pro Asp Pro Gly Thr Pro Leu Pro Pro Asp Pro Thr | | | |

340 345 350
 Ala Pro Ser Pro Arg His Gly His Pro Cys Xaa His Leu His Ser Glu
 355 360 365
 Glu Pro Ala Arg His Leu Ser Pro Ser Pro Pro Val Asp Ile Thr Val
 370 375 380
 Pro Gly Thr Ala Leu Pro Pro Pro Leu Gly Pro Ser Pro Ala Trp Arg
 385 390 395 400
 Val His His Tyr Val Arg Lys Ala Pro Ser Ala Pro Pro Lys Pro Ser
 405 410 415
 Pro Cys Leu Thr Glu Ala Cys Ile Phe Ile Ser Asp Tyr Ser Arg Thr
 420 425 430
 Ser Val

<210> 507
 <211> 303
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (165)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (280)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 507
 Glu Tyr Val Phe Pro Ala Lys Lys Lys Leu Gln Glu Tyr Arg Val Leu
 1 5 10 15
 Ile Thr Thr Leu Ile Thr Ala Gly Ser Trp Ser Arg Pro Ser Phe Pro
 20 25 30
 Leu Ile Thr Ser His Thr Ser Ser Ser Met Arg Leu Ala Thr Ala Trp
 35 40 45
 Ser Leu Arg Ser Leu Val Ala Ile Ala Gly Leu Met Glu Val Lys Glu
 50 55 60
 Thr Gly Asp Pro Gly Gly Gln Leu Val Leu Ala Gly Asp Pro Arg Gln

463

| | | | | | | |
|---|-----|----|-----|----|-----|-----|
| 65 | | 70 | | 75 | | 80 |
| Leu Gly Pro Val Leu Arg Ser Pro Leu Thr Gln Lys His Gly Leu Gly | | | | | | |
| | 85 | | 90 | | 95 | |
| Tyr Ser Leu Leu Glu Arg Leu Leu Thr Tyr Asn Ser Leu Tyr Lys Lys | | | | | | |
| | 100 | | 105 | | 110 | |
| Gly Pro Asp Gly Tyr Asp Pro Gln Phe Ile Thr Lys Leu Leu Arg Asn | | | | | | |
| | 115 | | 120 | | 125 | |
| Tyr Arg Ser His Pro Thr Ile Leu Asp Ile Pro Asn Gln Leu Tyr Tyr | | | | | | |
| | 130 | | 135 | | 140 | |
| Glu Gly Glu Leu Gln Ala Cys Ala Asp Val Val Asp Arg Glu Arg Phe | | | | | | |
| | 145 | | 150 | | 155 | 160 |
| Cys Arg Trp Ala Xaa Leu Pro Arg Gln Gly Phe Pro Ile Ile Phe His | | | | | | |
| | 165 | | 170 | | 175 | |
| Gly Val Met Gly Lys Asp Glu Arg Glu Gly Asn Ser Pro Ser Phe Phe | | | | | | |
| | 180 | | 185 | | 190 | |
| Asn Pro Glu Glu Ala Ala Thr Val Thr Ser Tyr Leu Lys Leu Leu Leu | | | | | | |
| | 195 | | 200 | | 205 | |
| Ala Pro Ser Ser Lys Lys Gly Lys Ala Arg Leu Ser Pro Arg Ser Val | | | | | | |
| | 210 | | 215 | | 220 | |
| Gly Val Ile Ser Pro Tyr Arg Lys Gln Val Glu Lys Ile Arg Tyr Cys | | | | | | |
| | 225 | | 230 | | 235 | 240 |
| Ile Thr Lys Leu Asp Arg Glu Leu Arg Gly Leu Asp Asp Ile Lys Asp | | | | | | |
| | 245 | | 250 | | 255 | |
| Leu Lys Val Gly Ser Val Glu Glu Phe Gln Gly Gln Glu Arg Ser Val | | | | | | |
| | 260 | | 265 | | 270 | |
| Ile Leu Ile Ser Thr Val Arg Xaa Ala Arg Ala Leu Cys Ser Trp Ile | | | | | | |
| | 275 | | 280 | | 285 | |
| Trp Thr Leu Ile Trp Val Ser Leu Arg Thr Pro Arg Gly Ser Met | | | | | | |
| | 290 | | 295 | | 300 | |

<210> 508

<211> 250

<212> PRT

<213> Homo sapiens

464

<220>

<221> SITE

<222> (16)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 508

Glu Gln Tyr Leu Pro Leu Thr Glu Glu Glu Leu Glu Lys Glu Ala Xaa
1 5 10 15

Lys Val Glu Gly Phe Asp Leu Val Gln Lys Pro Ser Tyr Tyr Val Arg
20 25 30

Leu Gly Ser Leu Ser Thr Lys Leu His Ser Arg Ala Tyr Gln Gln Ala
35 40 45

Leu Ser Arg Val Lys Glu Ala Lys Gln Lys Ser Gln Gln Thr Ile Ser
50 55 60

Gln Leu His Ser Thr Val His Leu Ile Glu Phe Ala Arg Lys Asn Val
65 70 75 80

Tyr Ser Ala Asn Gln Lys Ile Gln Asp Ala Gln Asp Lys Leu Tyr Leu
85 90 95

Ser Trp Val Glu Trp Lys Arg Ser Ile Gly Tyr Asp Asp Thr Asp Glu
100 105 110

Ser His Cys Ala Glu His Ile Glu Ser Arg Thr Leu Ala Ile Ala Arg
115 120 125

Asn Leu Thr Gln Gln Leu Gln Thr Thr Cys His Thr Leu Leu Ser Asn
130 135 140

Ile Gln Gly Val Pro Gln Asn Ile Gln Asp Gln Ala Lys His Met Gly
145 150 155 160

Val Met Ala Gly Asp Ile Tyr Ser Val Phe Arg Asn Ala Ala Ser Phe
165 170 175

Lys Glu Val Ser Asp Ser Leu Leu Thr Ser Ser Lys Gly Gln Leu Gln
180 185 190

Lys Met Lys Glu Ser Leu Asp Asp Val Met Asp Tyr Leu Val Asn Asn
195 200 205

Thr Pro Leu Asn Trp Leu Val Gly Pro Phe Tyr Pro Gln Leu Thr Glu
210 215 220

Ser Gln Asn Ala Gln Asp Gln Gly Ala Glu Met Asp Lys Ser Ser Gln
225 230 235 240

465

Glu Thr Gln Arg Ser Glu His Lys Thr His
 245 250

<210> 509

<211> 98

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (97)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 509

His Glu Leu Trp Gly Cys Gly Pro Val Thr Pro Arg Arg Thr Ala Pro
 1 5 10 15

Ser Gly Trp Ala Gln Ala Pro Leu Ser Asp Thr Ala Gln Val Tyr Met
 20 25 30

Glu Leu Gln Gly Leu Val Asp Pro Gln Ile Gln Leu Pro Leu Leu Ala
 35 40 45

Ala Arg Ser Thr Ser Cys Arg Ser Ser Leu Ile Ala Ser Gln Pro Gly
 50 55 60

Pro His Gln Lys Gly Arg Gln Gly Leu Arg Gly Asn Lys Ser Phe Leu
 65 70 75 80

Pro Ser Ser Trp Asn Cys Gln Asn Trp Thr Arg Gln Pro Leu Thr Ser
 85 90 95

Xaa Ser

<210> 510

<211> 392

<212> PRT

<213> Homo sapiens

<400> 510

Gly Ala Met Arg Gly Asp Arg Gly Arg Gly Arg Gly Arg Phe Gly
 1 5 10 15

Ser Arg Gly Gly Pro Gly Gly Gly Phe Arg Pro Phe Val Pro His Ile
 20 25 30

Pro Phe Asp Phe Tyr Leu Cys Glu Met Ala Phe Pro Arg Val Lys Pro
35 40 45

Ala Pro Asp Glu Thr Ser Phe Ser Glu Ala Leu Leu Lys Arg Asn Gln
50 55 60

Asp Leu Ala Pro Asn Ser Ala Glu Gln Ala Ser Ile Leu Ser Leu Val
65 70 75 80

Thr Lys Ile Asn Asn Val Ile Asp Asn Leu Ile Val Ala Pro Gly Thr
85 90 95

Phe Glu Val Gln Ile Glu Glu Val Arg Gln Val Gly Ser Tyr Lys Lys
100 105 110

Gly Thr Met Thr Thr Gly His Asn Val Ala Asp Leu Val Val Ile Leu
115 120 125

Lys Ile Leu Pro Thr Leu Glu Ala Val Ala Ala Leu Gly Asn Lys Val
130 135 140

Val Glu Ser Leu Arg Ala Gln Asp Pro Ser Glu Val Leu Thr Met Leu
145 150 155 160

Thr Asn Glu Thr Gly Phe Glu Ile Ser Ser Ser Asp Ala Thr Val Lys
165 170 175

Ile Leu Ile Thr Thr Val Pro Pro Asn Leu Arg Lys Leu Asp Pro Glu
180 185 190

Leu His Leu Asp Ile Lys Val Leu Gln Ser Ala Leu Ala Ala Ile Arg
195 200 205

His Ala Arg Trp Phe Glu Glu Asn Ala Ser Gln Ser Thr Val Lys Val
210 215 220

Leu Ile Arg Leu Leu Lys Asp Leu Arg Ile Arg Phe Pro Gly Phe Glu
225 230 235 240

Pro Leu Thr Pro Trp Ile Leu Asp Leu Leu Gly His Tyr Ala Val Met
245 250 255

Asn Asn Pro Thr Arg Gln Pro Leu Ala Leu Asn Val Ala Tyr Arg Arg
260 265 270

Cys Leu Gln Ile Leu Ala Ala Gly Leu Phe Leu Pro Gly Ser Val Gly
275 280 285

Ile Thr Asp Pro Cys Glu Ser Gly Asn Phe Arg Val His Thr Val Met
290 295 300

Thr Leu Glu Gln Gln Asp Met Val Cys Tyr Thr Ala Gln Thr Leu Val
305 310 315 320

Arg Ile Leu Ser His Gly Gly Phe Arg Lys Ile Leu Gly Gln Glu Gly
325 330 335

Asp Ala Ser Tyr Leu Ala Ser Glu Ile Ser Thr Trp Asp Gly Val Ile
340 345 350

Val Thr Pro Ser Glu Lys Ala Tyr Glu Lys Pro Pro Glu Lys Lys Glu
355 360 365

Gly Glu Glu Glu Glu Glu Asn Thr Glu Glu Pro Pro Gln Gly Glu Glu
370 375 380

Glu Glu Ser Met Glu Thr Gln Glu
385 390

<210> 511
<211> 72
<212> PRT
<213> Homo sapiens

<400> 511
His Gly Gly Gly Lys Gly Arg Gln Val Gly Leu His Ser Val Gln Arg
1 5 10 15

Pro Ala Arg Arg Glu Thr Ala Ala Ser Trp Gly Leu Cys Val Lys Ile
20 25 30

Pro Asp Leu Gly Val Ala Phe Val Tyr Lys Met Gln Glu Gly Lys Pro
35 40 45

Val Pro Asp Ser Ser Arg Gln His Ala Gln Leu Ser Gly Ser Pro Val
50 55 60

Ser Gln Gly Leu Ser Leu Pro Leu
65 70

<210> 512
<211> 181
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (14)

(221) SITE

<222> (33)

<223> xaa equals any of the naturally occurring L-amino acids

<221> SITE

<222> (135)

<223> Xaa equals any of the naturally occurring L-amino acids

Gly Trp Cys Ser Cys Ala His Ser Ser Ala Trp Pro Gly Xaa Trp Gly
1 5 10 15

Ala Ser Gly Ile Pro Gln Gln Ala Pro Met Thr Val Cys Asp Gln Ala
20 25 30

Xaa Pro Val Thr Phe Leu Leu Leu His Leu Glu Gly Gly Asp Ile His
35 40 45

Thr Val Ser His Leu Ser Ser Pro Pro Pro Gly Val Ala His Arg Met
50 55 60

Gly Thr Gly Gly Ser Arg Asn Pro Asn Pro Ala Trp Leu Gly Gly Ala
65 70 75 80

Leu Leu Val Arg Gly Arg Pro Ala Ser Leu Ala Pro Trp Gly His Ser
85 90 95

Trp Lys Arg Gly Leu Ala His Ala Pro Leu Arg Ala Gly Thr Cys Thr
100 105 110

Gly His Thr Arg His Ser Ala Cys Trp Asn Arg Trp Leu Cys Ser Cys
115 120 125

Ser Gly Pro Arg Ala Ala Xaa Leu Arg Pro Cys Thr Ser His Met His
130 135 140

Trp Thr Arg Ala Glu Thr Pro Val Cys Tyr Arg Ala Leu Val Leu Cys
145 150 155 160

Gly Pro Gly Ala Thr Ala Gln Ser Ser Gln Trp Arg Ser Thr Pro Leu
165 170 175

Asp Ser Ile Phe Phe
180

<210> 513
<211> 202
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (15)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 513
Leu Gly Asp Thr Ile Glu Gly Thr Pro Ala Gly Thr Val Pro Xaa Phe
1 5 10 15
Pro Gly Arg Pro Thr Arg Ala Ile Met Ala Gln Asp Gln Gly Glu Lys
20 25 30
Glu Asn Pro Met Arg Glu Leu Arg Ile Arg Lys Leu Cys Leu Asn Ile
35 40 45
Cys Val Gly Glu Ser Gly Asp Arg Leu Thr Arg Ala Ala Lys Val Leu
50 55 60
Glu Gln Leu Thr Gly Gln Thr Pro Val Phe Ser Lys Ala Arg Tyr Thr
65 70 75 80
Val Arg Ser Phe Gly Ile Arg Arg Asn Glu Lys Ile Ala Val His Cys
85 90 95
Thr Val Arg Gly Ala Lys Ala Glu Glu Ile Leu Glu Lys Gly Leu Lys
100 105 110
Val Arg Glu Tyr Glu Leu Arg Lys Asn Asn Phe Ser Asp Thr Gly Asn
115 120 125
Phe Gly Phe Gly Ile Gln Glu His Ile Asp Leu Gly Ile Lys Tyr Asp
130 135 140
Pro Ser Ile Gly Ile Tyr Gly Leu Asp Phe Tyr Val Val Leu Gly Arg
145 150 155 160
Pro Gly Phe Ser Ile Ala Asp Lys Lys Arg Arg Thr Gly Cys Ile Gly
165 170 175
Ala Lys His Arg Ile Ser Lys Glu Glu Ala Met Arg Trp Phe Gln Gln
180 185 190
Lys Tyr Asp Gly Ile Ile Leu Pro Gly Lys
195 200

<210> 514
<211> 63
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (2)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (35)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 514
Xaa Xaa Lys Asn Xaa Ile Thr Pro Lys Glu Glu Ser Pro Pro His Xaa
1 5 10 15
Ala Leu Leu Ser Lys Cys Leu Leu Thr Pro Ser Pro Lys Met Pro Pro
20 25 30
Ile Leu Xaa Val Met Ala Ala Leu Gly Phe Glu Arg Arg Glu Phe Gly
35 40 45
Ser Thr Ser Val Glu Arg Val Gln Ser Arg Gln Leu Asp Cys Phe
50 55 60

<210> 515
<211> 218
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (151)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (209)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (211)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 515
Ser Leu Ala Arg Gly Cys Gln Arg Pro Asp Ala Val Leu Tyr Ala Arg
1 5 10 15
His Tyr Asn Ile Pro Val Ile His Ala Phe Arg Arg Ala Val Asp Asp
20 25 30
Pro Gly Leu Val Phe Asn Gln Leu Pro Lys Met Leu Tyr Pro Glu Tyr
35 40 45
His Lys Val His Gln Met Met Arg Glu Gln Ser Ile Leu Ser Pro Ser
50 55 60
Pro Tyr Glu Gly Tyr Arg Ser Leu Pro Arg His Gln Leu Leu Cys Phe
65 70 75 80
Lys Glu Asp Cys Gln Ala Val Phe Gln Asp Leu Glu Gly Val Glu Lys
85 90 95
Val Phe Gly Val Ser Leu Val Leu Val Leu Ile Gly Ser His Pro Asp
100 105 110
Leu Ser Phe Leu Pro Gly Ala Gly Ala Asp Phe Ala Val Asp Pro Asp
115 120 125
Gln Pro Leu Ser Ala Lys Arg Asn Pro Ile Asp Val Asp Pro Phe Thr
130 135 140
Tyr Gln Ser Thr Arg Gln Xaa Gly Leu Tyr Ala Met Gly Pro Leu Ala
145 150 155 160
Gly Asp Asn Phe Val Arg Phe Val Gln Gly Gly Ala Leu Ala Val Ala
165 170 175
Ser Ser Leu Leu Arg Lys Glu Gln Asn His Leu His Arg Gln Pro Trp
180 185 190

472

Ser Ser Leu Arg Gly Ile His Pro Leu Ile Asp Leu Lys Ser Gly Val
195 200 205

Xaa Pro Xaa Leu Val Lys Leu Thr Ala Gln
210 215

<210> 516
<211> 41
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (22)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 516
Asn Gly Arg Pro Asp Ser Thr Gly Pro Ala Ile Pro Gly Ile Leu Ser
1 5 10 15

Trp Gly Phe Glu Thr Xaa Leu Arg Asp Arg Glu Thr Asp Pro Arg Asn
20 25 30

Val Leu Asn Cys Asn Gly Pro His Thr
35 40

<210> 517
<211> 250
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (118)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (161)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (204)
<223> Xaa equals any of the naturally occurring L-amino acids

473

<400> 517

Gly Phe Asn Arg Ser Phe Cys Gly Arg Asn Ala Thr Val Tyr Gly Lys
 1 5 10 15

Gly Val Tyr Phe Ala Arg Arg Ala Ser Leu Ser Val Gln Asp Arg Tyr
 20 25 30

Ser Pro Pro Asn Ala Asp Gly His Lys Ala Val Phe Val Ala Arg Val
 35 40 45

Leu Thr Gly Asp Tyr Gly Gln Gly Arg Arg Gly Leu Arg Ala Pro Pro
 50 55 60

Leu Arg Gly Pro Gly His Val Leu Leu Arg Tyr Asp Ser Ala Val Asp
 65 70 75 80

Cys Ile Cys Gln Pro Ser Ile Phe Val Ile Phe His Asp Thr Gln Ala
 85 90 95

Leu Pro Thr His Leu Ile Thr Cys Glu Ala Arg Ala Pro Arg Phe Pro
 100 105 110

Arg Arg Pro Leu Trp Xaa Pro Gly Pro Leu Pro Arg His Leu Thr Glu
 115 120 125

Gly Ala Thr Leu Trp Pro Pro Ala Ser Gln Ala Pro Ser Ser Ala Gln
 130 135 140

Ala Asp Ala Pro Arg Pro Gln Leu Trp Pro Pro Glu Leu Ser Pro Gly
 145 150 155 160

Xaa Pro Cys Leu Pro Leu Arg Ala Pro Glu Gly Gly Val Gly Asp Gly
 165 170 175

Gly Gln Gln Arg Pro Arg Gly Ala Gly Leu Gly Pro Ser Leu Gly Arg
 180 185 190

Pro His His Gln Gly Ser Ala Glu Pro Arg Arg Xaa His Arg Pro Pro
 195 200 205

Ala Ala Pro Arg Pro Arg Pro Ser Arg Leu Cys Cys Leu Asn Lys Arg
 210 215 220

Glu Arg Glu Pro Arg Arg Lys Gly Pro Gly Lys Lys Lys Lys Lys Lys
 225 230 235 240

Lys Lys Lys Lys Lys Lys Lys Lys Lys Lys
 245 250

<210> 518
 <211> 100
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (3)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 518
 Asn Pro Xaa Lys Lys Leu Xaa Ile Leu Ile Lys Trp Pro Pro Pro Phe
 1 5 10 15
 Pro Pro Ser Phe Pro Pro Ser Pro Asn Ser Leu Ser Ser Ser Ser Phe
 20 25 30
 Pro Pro Pro Leu Ser Leu Phe Ser Pro Ser Phe Thr Phe Leu Ile Ser
 35 40 45
 Val Lys Leu Glu Arg Phe Glu Ile Pro Ile Lys Val Arg Leu Ser Pro
 50 55 60
 Glu Pro Trp Thr Pro Glu Thr Gly Leu Val Thr Asp Ala Phe Lys Leu
 65 70 75 80
 Lys Arg Lys Glu Leu Arg Asn His Tyr Leu Lys Asp Ile Glu Arg Met
 85 90 95
 Tyr Gly Gly Lys
 100

<210> 519
 <211> 60
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (5)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE

<222> (17)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 519

His Glu Asp Gly Xaa Leu Met Gly Cys Arg His Arg Trp His Pro Arg
1 5 10 15

Xaa Val Pro Phe His Gln Thr Ser Pro Lys Thr Glu Leu Glu Ser Thr
20 25 30

Ile Phe Gly Ser Pro Arg Leu Ala Ser Gly Leu Phe Pro Glu Trp Gln
35 40 45

Ser Trp Gly Arg Met Glu Asn Leu Ala Ser Tyr Arg
50 55 60

<210> 520

<211> 120

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (25)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 520

Ser His Pro Tyr Ala Pro Ser Cys Gly Leu Arg Gly Pro Gly Ala Ala
1 5 10 15

Ser Arg Ala Arg Thr Arg Glu Arg Xaa Pro Gln Ala Glu Ala Glu Ala
20 25 30

Arg Ser Thr Pro Gly Pro Ala Gly Ser Arg Leu Gly Pro Glu Thr Phe
35 40 45

Arg Gln Arg Phe Arg Gln Phe Arg Tyr Gln Asp Ala Ala Gly Pro Arg
50 55 60

Glu Ala Phe Arg Gln Leu Arg Glu Leu Ser Arg Gln Trp Leu Arg Pro
65 70 75 80

Asp Ile Arg Thr Lys Glu Gln Ile Val Glu Met Leu Val Gln Glu Gln
85 90 95

Leu Leu Ala Ile Leu Pro Glu Ala Ala Arg Ala Arg Arg Ile Arg Arg
100 105 110

Arg Thr Asp Val Arg Ile Thr Gly

115

120

<210> 521

<211> 96

<212> PRT

<213> Homo sapiens

<400> 521

Gly His Gln Thr Val Ser Pro Ser Thr Gly Ser Arg Val Thr Arg Met
1 5 10 15

Phe Ser Leu Ile Ser Phe Ser His Val Phe Ile Lys Asp Ile Cys Lys
20 25 30

Leu Pro Lys Asp Glu Gly Thr Cys Arg Asp Phe Ile Leu Lys Trp Tyr
35 40 45

Tyr Asp Pro Asn Thr Lys Ser Cys Ala Arg Phe Trp Tyr Gly Gly Cys
50 55 60

Gly Gly Asn Glu Asn Lys Phe Gly Ser Gln Lys Glu Cys Glu Lys Val
65 70 75 80

Cys Ala Pro Val Leu Ala Lys Pro Gly Val Ile Ser Val Met Gly Thr
85 90 95

<210> 522

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 522

Asn Ser Gly Phe Arg Pro Lys Asn Pro Val Gly Arg Gly Gly Glu Pro
1 5 10 15

Glu Xaa Cys Gly Gly Ala Gly Gly Leu Gly Cys Thr Leu Val Trp Gly
20 25 30

Gly Thr Gly Ala Ala Val Val Thr Gly Val Val Trp Leu Leu Pro

477

35 40 45
 Asn Gly Gly Val Gly Val Gly Leu Leu Gly Pro Gln Ser Pro Val Gly
 50 55 60
 Gly Ser Asp Ser Ala Pro Tyr Ser Leu His Pro Ala Gly Arg Thr Trp
 65 70 75 80
 Gly Leu Arg Ser Glu Cys Ile Pro Pro Leu Ser Phe Asn Leu Ser Cys
 85 90 95
 Arg Thr His Ser Gly Pro Gly Ala Arg Leu Gly Glu Ala Gly Pro Asn
 100 105 110
 Tyr Gly Ser Arg Glu Leu Gln Val Pro Thr
 115 120

<210> 523
 <211> 94
 <212> PRT
 <213> Homo sapiens

<400> 523
 Leu Ile Pro Gln Val Cys Cys Lys His Ser Met Glu Asp Thr Asp Asp
 1 5 10 15
 Ser Leu Val Leu Val Phe Leu Ser Ala Val Asn Val Gln Gln Phe Ala
 20 25 30
 Gln Glu Leu Gly Asp His Ile Cys Leu Ser Gly Gln Gly Ser Glu Val
 35 40 45
 His Trp Asn Leu Leu Arg Asn Leu Phe Val Lys Thr Ile Val Asn Asn
 50 55 60
 Tyr Cys Ile Phe Leu Gln Lys Tyr Ile Leu Glu Asn Cys Ile Leu Ser
 65 70 75 80
 Ile Lys Val Phe Leu Cys Lys Lys Lys Lys Lys Lys Leu Val
 85 90

<210> 524
 <211> 93
 <212> PRT
 <213> Homo sapiens

<220>

<221> SITE
 <222> (78)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (86)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (93)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 524
 Ser Ala Val Met Gly Arg Lys Lys Lys Lys Gln Leu Lys Pro Trp Cys
 1 5 10 15
 Trp Tyr Cys Asn Arg Asp Phe Asp Asp Glu Lys Ile Leu Ile Gln His
 20 25 30
 Gln Lys Ala Lys His Phe Lys Cys His Ile Cys His Lys Lys Leu Tyr
 35 40 45
 Thr Gly Pro Gly Leu Ala Ile His Cys Met Gln Val His Lys Glu Thr
 50 55 60
 Ile Asp Ala Val Pro Asn Ala Tyr Leu Gly Glu Gln Thr Xaa Ile Gly
 65 70 75 80
 Asn Ile Trp Tyr Gly Xaa Tyr Ser Arg Lys Arg Tyr Xaa
 85 90

<210> 525
 <211> 324
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (323)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 525
 Asp Leu Arg Leu Ser Arg Pro Glu Ala Val Glu Ala Glu Ala Met Met
 1 5 10 15
 Ala Ala Met Ala Thr Ala Arg Val Arg Met Gly Pro Arg Cys Ala Gln
 20 25 30

Ala Leu Trp Arg Met Pro Trp Leu Pro Val Phe Leu Ser Leu Ala Ala
 35 40 45
 Ala Ala Ala Ala Ala Ala Ala Glu Gln Gln Val Pro Leu Val Leu Trp
 50 55 60
 Ser Ser Asp Arg Asp Leu Trp Ala Pro Ala Ala Asp Thr His Glu Gly
 65 70 75 80
 His Ile Thr Ser Asp Leu Gln Leu Ser Thr Tyr Leu Asp Pro Ala Leu
 85 90 95
 Glu Leu Gly Pro Arg Asn Val Leu Leu Phe Leu Gln Asp Lys Leu Ser
 100 105 110
 Ile Glu Asp Phe Thr Ala Tyr Gly Gly Val Phe Gly Asn Lys Gln Asp
 115 120 125
 Ser Ala Phe Ser Asn Leu Glu Asn Ala Leu Asp Leu Ala Pro Ser Ser
 130 135 140
 Leu Val Leu Pro Ala Val Asp Trp Tyr Ala Val Ser Thr Leu Thr Thr
 145 150 155 160
 Tyr Leu Gln Glu Lys Leu Gly Ala Ser Pro Leu His Val Asp Leu Ala
 165 170 175
 Thr Leu Arg Glu Leu Lys Leu Asn Ala Ser Leu Pro Ala Leu Leu Leu
 180 185 190
 Ile Arg Leu Pro Tyr Thr Ala Ser Ser Gly Leu Met Ala Pro Arg Glu
 195 200 205
 Val Leu Thr Gly Asn Asp Glu Val Ile Gly Gln Val Leu Ser Thr Leu
 210 215 220
 Lys Ser Glu Asp Val Pro Tyr Thr Ala Ala Leu Thr Ala Val Arg Pro
 225 230 235 240
 Ser Arg Val Ala Arg Asp Val Ala Val Val Ala Gly Gly Leu Gly Arg
 245 250 255
 Gln Leu Leu Gln Lys Gln Pro Val Ser Pro Val Ile His Pro Pro Val
 260 265 270
 Ser Tyr Asn Asp Thr Ala Pro Arg Ile Leu Phe Trp Ala Gln Asn Phe
 275 280 285
 Ser Val Ala Tyr Lys Asp Gln Trp Glu Asp Leu Thr Pro Leu Thr Phe
 290 295 300

480

Gly Val Gln Glu Leu Asn Leu Thr Gly Ser Phe Trp Asn Asp Ser Phe
 305 310 315 320

Ala Ser Xaa His

<210> 526

<211> 66

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (2)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 526

Phe Xaa Val Ser Trp Thr Trp Lys Gln Val Ser Glu Phe Pro Gly Asp
 1 5 10 15

Gln Arg Asp Glu Val Leu Gln Leu Pro Pro Ser Ser Cys Asn Leu Val
 20 25 30

Ser Ser Gly Ala Gly Gly Glu Pro Glu Lys Leu Ala Ser Tyr Ile Thr
 35 40 45

Ser Leu Trp Leu Phe Phe Ile Cys Lys Thr Arg Ile Ile Leu Asn Cys
 50 55 60

Lys Gly
 65

<210> 527

<211> 62

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (40)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 527

Asn Thr Gln Leu Trp Phe Leu Cys Phe Pro Asn Cys Lys Ala Ala Asp
 1 5 10 15

481

Asn Lys Thr Pro Gly Phe His Val Ser Ser Ala Met Ser Thr Leu Thr
 20 25 30

Gln Ile Leu Lys Gln Asn Ser Xaa Asn Ala Val Leu Arg Ile Gln Leu
 35 40 45

Leu Leu Lys Pro Ile Ser Ile Cys Ile Ile Thr Thr Asn Ile
 50 55 60

<210> 528

<211> 122

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (104)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (105)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 528

Tyr Asn Lys Ile Glu Ile Met His Leu Val Met Trp Pro Thr Ser Leu
 1 5 10 15

Leu Thr Thr Met Asp Cys Phe Gln Gln Gln Leu Ile Phe Trp Ser Val
 20 25 30

Leu Arg Gly Ala Cys Met Ser Phe Val Thr Ser Gly Ser Thr Pro Ala
 35 40 45

Val Lys Tyr Cys Phe His Leu Pro Leu Gln Lys Ala Ser Cys Leu Leu
 50 55 60

Thr Ser Thr Ala Lys Ala Leu Phe Trp Thr Gly Tyr Leu Ile Lys Xaa
 65 70 75 80

Ile Ser Val Arg Leu Cys Ser Val Ile Pro Ser Glu Pro Arg Phe Val
 85 90 95

Ser Lys Ala Thr Val Leu Ser Xaa Xaa Pro Cys Val Trp Gly Gln Val

482

100 105 110
 Ala Ile Pro Pro Met Ser Leu Val Ile Leu
 115 120

<210> 529
 <211> 182
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (25)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 529
 Asp Arg Thr Arg Leu Ser Gln Ala Ser Thr Pro Thr Pro Val Cys Trp
 1 5 10 15
 Gly Leu Leu Gln Pro Pro Pro Trp Xaa Glu Ala Trp Tyr Arg Leu Thr
 20 25 30
 His Arg Gly Leu Cys Gln Val Arg Phe Cys Arg Trp Ser Gln Ala Leu
 35 40 45
 Pro Glu Ala Arg Gly Gly Ala Trp Ala Gly Ser Pro Gly Glu Gly Gln
 50 55 60
 Ala Gly Pro Arg Leu His Thr His Ile Gln Pro Ala Gly Leu Ser Ala
 65 70 75 80
 Val Leu Ser Pro Ser Leu Ser Ser Pro Ser Ser Ala Val Thr Leu Ser
 85 90 95
 Ser Pro Ser Leu Pro Ala Ser Pro Pro Ala Ala Pro Pro Val Lys Arg
 100 105 110
 Met Thr Lys Asp Leu Ser Tyr Ala Gly Ser Lys Asn Gln Asn Phe Leu
 115 120 125
 Leu Ala Phe Ser Phe Val Ala Ser Pro Ala Pro Ala Leu Pro Val Ser
 130 135 140
 His Pro Gly Pro Arg Leu Glu Ala Ser Leu His Leu Ser Tyr Cys Phe
 145 150 155 160
 Lys Pro Lys Phe Thr Val Ser Val Gly Gly Gln Asp Leu Leu Ser Pro
 165 170 175

Pro Leu Leu His Pro Pro
180

<210> 530

<211> 183

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (79)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (81)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 530

Ala Leu Val Leu Gly Xaa Lys Ser Val Arg Met Ala Ser Ser Arg Met
1 5 10 15

Thr Arg Arg Asp Pro Leu Thr Asn Lys Val Ala Leu Val Thr Ala Ser
20 25 30

Thr Asp Gly Ile Gly Phe Ala Ser Pro Gly Val Trp Pro Arg Thr Gly
35 40 45

Pro Arg Gly Arg Gln Gln Pro Glu Ala Ala Glu Cys Gly Pro Gly Gly
50 55 60

Gly Thr Leu Gln Gly Glu Gly Leu Ser Val Thr Gly Thr Cys Xaa Xaa
65 70 75 80

Xaa Gly Lys Ala Glu Asp Arg Glu Arg Leu Val Ala Thr Ala Val Lys
85 90 95

Leu His Gly Gly Ile Asp Ile Leu Val Ser Asn Ala Ala Val Asn Pro
100 105 110

[illegible]

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<210> 531
<211> 129
<212> PRT
<213> Homo sapiens
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<220>
<221> SITE
<222> (89)
<223> Xaa equals any of the naturally occurring L-amino acids
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<220>
<221> SITE
<222> (103)
<223> Xaa equals any of the naturally occurring L-amino acids
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<400> 531
Asn Ser Ala Pro Leu Ser Pro Thr Gly Leu Gly Gln Gly His Thr Gly
 1             5             10             15
His Val Arg Phe Leu Ala Ala Val Gln Leu Pro Asp Gly Phe Asn Leu
      20             25             30
Leu Cys Pro Thr Pro Pro Pro Pro Asp Thr Gly Pro Glu Lys Leu
      35             40             45
Pro Ser Leu Glu His Arg Asp Ser Pro Trp His Arg Gly Pro Ala Pro
      50             55             60
Ala Arg Pro Lys Met Leu Val Ile Ser Gly Gly Asp Gly Tyr Glu Asp
 65             70             75             80
Phe Arg Leu Ser Ser Gly Gly Gly Xaa Ala Val Arg Leu Trp Val Glu
      85             90             95

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485

Thr Thr Ala Gln Thr Thr Xaa Ser Cys Gly Gly Cys Asp Pro Val Cys
 100 105 110

Arg Gly Pro Gly Leu Ala Arg Pro Pro Ala Phe Ser Leu Leu Ala Ser
 115 120 125

Pro

<210> 532

<211> 91

<212> PRT

<213> Homo sapiens

<400> 532

Gly Ala Ile Ala Ser Ser Gly Pro Thr Gly Gly Arg Val Arg Lys His
 1 5 10 15

Gln Leu Leu Pro Gly Ala Val Arg Glu Trp Glu Gln Leu Trp Ala Pro
 20 25 30

His Phe Arg Gln Val Leu Pro Lys Pro Ser Asp Ala Val Arg Pro Gly
 35 40 45

Leu Pro Val Val Leu Phe Arg Leu Cys Phe Gln Asn Ala Phe Ile Ser
 50 55 60

Ser Val Pro Phe Gly Pro His Lys Ser Pro Trp Gly Val Gly Gly Gly
 65 70 75 80

Leu Cys Arg His Pro His Phe Lys Ala Gly Ser
 85 90

<210> 533

<211> 67

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (63)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 533

Asn Leu Cys Gln Val Gln Pro Thr Arg Leu Tyr Ser Ser Leu His Ser
 1 5 10 15

486

Gly Leu His His Val Arg Gln Val Thr Gln Lys Ser Tyr Lys Val Ser
 20 25 30

Thr Ser Gly Pro Arg Ala Phe Ser Ser Arg Ser Tyr Thr Ser Gly Pro
 35 40 45

Gly Ser Arg Ile Ser Ser Ser Ala Phe Ser Arg Val Gly Gly Xaa Ser
 50 55 60

Gly Gly Ala
 65

<210> 534

<211> 144

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (140)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (141)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 534

Phe Asn Arg Arg Tyr Pro Lys Ile Gln Phe Ser Leu Ser Thr Gly Pro
 1 5 10 15

Ser Gly Thr Met Leu Asp Gly Val Leu Glu Gly Lys Leu Asn Ala Ala
 20 25 30

Phe Ile Asp Gly Pro Ile Asn His Thr Ala Ile Asp Gly Ile Pro Val
 35 40 45

Tyr Arg Glu Glu Leu Met Ile Val Thr Pro Gln Gly Tyr Ala Pro Val
 50 55 60

Thr Arg Ala Ser Gln Val Asn Gly Ser Asn Ile Tyr Ala Phe Arg Ala
 65 70 75 80

Asn Cys Ser Tyr Arg Arg His Phe Glu Ser Trp Phe His Ala Asp Gly
 85 90 95

Ala Ala Pro Gly Thr Ile His Glu Met Glu Ser Tyr His Gly Met Leu
 100 105 110

Ala Cys Val Ile Ala Gly Ala Gly Ile Ala Leu Ile Pro Arg Ser Met
115 120 125

Leu Glu Ser Met Pro Gly His His Gln Val Glu Xaa Xaa Ala Val Ser
130 135 140

<210> 535
<211> 175
<212> PRT
<213> Homo sapiens

<400> 535

Arg Ala Pro Ala Arg Ile Ser Gly Gly Gly Ser Ala Met Val Gly Gly
1 5 10 15

Gly Gly Val Gly Gly Gly Leu Leu Glu Asn Ala Asn Pro Leu Ile Tyr
20 25 30

Gln Arg Ser Gly Glu Arg Pro Val Thr Ala Gly Glu Glu Asp Glu Gln
35 40 45

Val Pro Asp Ser Ile Asp Ala Arg Glu Ile Phe Asp Leu Ile Arg Ser
50 55 60

Ile Asn Asp Pro Glu His Pro Leu Thr Leu Glu Leu Asn Val Val
65 70 75 80

Glu Gln Val Arg Val Gln Val Ser Asp Pro Glu Ser Thr Val Ala Val
85 90 95

Ala Phe Thr Pro Thr Ile Pro His Cys Ser Met Ala Thr Leu Ile Gly
100 105 110

Leu Ser Ile Lys Val Lys Leu Leu Arg Ser Leu Pro Gln Arg Phe Lys
115 120 125

Met Asp Val His Ile Thr Pro Gly Thr His Ala Ser Glu His Ala Val
130 135 140

Asn Lys Gln Leu Ala Asp Lys Glu Arg Val Ala Ala Ala Leu Glu Asn
145 150 155 160

Thr His Leu Leu Glu Val Val Asn Gln Cys Leu Ser Ala Arg Ser
165 170 175

<210> 536
<211> 148
<212> PRT
<213> Homo sapiens

<400> 536
Gly Trp His Arg Thr His His Arg Gly Arg His Gln Ala Arg Glu Ala
1 5 10 15
Glu Glu Glu Ala Trp Ala Ala Ala Glu Pro Ile Lys Lys Val Arg Lys
20 25 30
Ser Leu Ala Leu Asp Ile Val Asp Glu Asp Val Lys Leu Met Met Ser
35 40 45
Thr Leu Pro Lys Ser Leu Ser Leu Pro Thr Thr Ala Pro Ser Asn Ser
50 55 60
Ser Ser Leu Thr Leu Ser Gly Ile Lys Glu Asp Asn Ser Leu Leu Asn
65 70 75 80
Gln Gly Phe Leu Gln Ala Lys Pro Glu Lys Ala Ala Val Ala Gln Lys
85 90 95
Pro Arg Ser His Phe Thr Thr Pro Ala Pro Met Ser Ser Ala Trp Lys
100 105 110
Thr Val Ala Cys Gly Gly Thr Arg Asp Gln Leu Phe Met Gln Glu Lys
115 120 125
Ala Arg Gln Leu Leu Gly Arg Leu Lys Pro Ser His Thr Ser Arg Thr
130 135 140
Leu Ile Leu Ser
145

<210> 537
<211> 70
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (41)
<223> Xaa equals any of the naturally occurring L-amino acids
<220>

489

<221> SITE

<222> (42)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 537

Arg Pro Thr Arg Ser Ala Trp Trp Gly Arg Leu Leu Ser Arg Val Ser
 1 5 10 15

Pro Gln Pro Arg Pro Ala Ser Pro Ser Val Ser Thr Arg Asn Gln Leu
 20 25 30

Pro Glu Ala Arg Arg Gly Val Glu Xaa Xaa Glu Cys Glu Glu Thr Ala
 35 40 45

Ala Ser Ala Glu Arg Ala Gly Pro Pro Arg Ala Leu Val Phe Gly Ala
 50 55 60

Gln Ser Arg Ser Pro Gly
 65 70

<210> 538

<211> 206

<212> PRT

<213> Homo sapiens

<400> 538

Gly Glu Val Ser Ala Ser Gly Ile Ala Arg Arg Gly Gly Pro Met Ala
 1 5 10 15

Pro Leu Gly Gly Ala Pro Arg Leu Val Leu Leu Phe Ser Gly Lys Arg
 20 25 30

Lys Ser Gly Lys Asp Phe Val Thr Glu Ala Leu Gln Ser Arg Leu Gly
 35 40 45

Ala Asp Val Cys Ala Val Leu Arg Leu Ser Gly Pro Leu Lys Glu Gln
 50 55 60

Tyr Ala Gln Glu His Gly Leu Asn Phe Gln Arg Leu Leu Asp Thr Ser
 65 70 75 80

Thr Tyr Lys Glu Ala Phe Arg Lys Asp Met Ile Arg Trp Gly Glu Glu
 85 90 95

Lys Arg Gln Ala Asp Pro Gly Phe Phe Cys Arg Lys Ile Val Glu Gly
 100 105 110

Ile Ser Gln Pro Ile Trp Leu Val Ser Asp Thr Arg Arg Val Ser Asp
 115 120 125

Ile Gln Trp Phe Arg Glu Ala Tyr Gly Ala Val Thr Gln Thr Val Arg
130 135 140

Val Val Ala Leu Glu Gln Ser Arg Gln Gln Arg Gly Trp Val Phe Thr
145 150 155 160

Pro Gly Val Asp Asp Ala Glu Ser Glu Cys Gly Leu Asp Asn Phe Gly
165 170 175

Asp Phe Asp Trp Val Ile Glu Asn His Gly Val Glu Gln Arg Leu Glu
180 185 190

Glu Gln Leu Glu Asn Leu Ile Glu Phe Ile Arg Ser Arg Leu
195 200 205

<210> 539
<211> 350
<212> PRT
<213> Homo sapiens

<400> 539
Ser Thr Leu Ile Ala Phe Ile Val Ile Ser Thr Leu Phe Pro Leu Leu
1 5 10 15

Asp Met Thr Glu Ile Tyr Phe Ser Leu Leu Asp Glu Ile Val Asp Thr
20 25 30

Leu Gly Glu Gly Ala Phe Gly Lys Val Val Glu Cys Ile Asp His Lys
35 40 45

Ala Gly Gly Arg His Val Ala Val Lys Ile Val Lys Asn Val Asp Arg
50 55 60

Tyr Cys Glu Ala Ala Arg Ser Glu Ile Gln Val Leu Glu His Leu Asn
65 70 75 80

Thr Thr Asp Pro Asn Ser Thr Phe Arg Cys Val Gln Met Leu Glu Trp
85 90 95

Phe Glu His His Gly His Ile Cys Ile Val Phe Glu Leu Leu Gly Leu
100 105 110

Ser Thr Tyr Asp Phe Ile Lys Glu Asn Gly Phe Leu Pro Phe Arg Leu
115 120 125

Asp His Ile Arg Lys Met Ala Tyr Gln Ile Cys Lys Ser Val Asn Phe
130 135 140

Leu His Ser Asn Lys Leu Thr His Thr Asp Leu Lys Pro Glu Asn Ile
145 150 155 160

Leu Phe Val Gln Ser Asp Tyr Thr Glu Ala Tyr Asn Pro Lys Ile Lys
165 170 175

Arg Asp Glu Arg Thr Leu Ile Asn Pro Asp Ile Lys Val Val Asp Phe
180 185 190

Gly Ser Ala Thr Tyr Asp Asp Glu His His Ser Thr Leu Val Ser Thr
195 200 205

Arg His Tyr Arg Ala Pro Glu Val Ile Leu Ala Leu Gly Trp Ser Gln
210 215 220

Pro Cys Asp Val Trp Ser Ile Gly Cys Ile Leu Ile Glu Tyr Tyr Leu
225 230 235 240

Gly Phe Thr Val Phe Pro Thr His Asp Ser Lys Glu His Leu Ala Met
245 250 255

Met Glu Arg Ile Leu Gly Pro Leu Pro Lys His Met Ile Gln Lys Thr
260 265 270

Arg Lys Arg Lys Tyr Phe His His Asp Arg Leu Asp Trp Asp Glu His
275 280 285

Ser Ser Ala Gly Arg Tyr Val Ser Arg Arg Cys Lys Pro Leu Lys Glu
290 295 300

Phe Met Leu Ser Gln Asp Val Glu His Glu Arg Leu Phe Asp Leu Ile
305 310 315 320

Gln Lys Met Leu Glu Tyr Asp Pro Ala Lys Arg Ile Thr Leu Arg Glu
325 330 335

Ala Leu Lys His Pro Phe Phe Asp Leu Leu Lys Lys Ser Ile
340 345 350

<210> 540

<211> 324

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (56)
 <223> xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (297)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (304)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (305)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (317)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (321)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 540
 Gln Ala Thr Met Gly Asn Val Leu Ala Ala Ser Ser Pro Pro Ala Gly
 1 5 10 15
 Pro Pro Pro Pro Pro Ala Pro Ala Leu Val Gly Leu Pro Pro Pro Pro
 20 25 30
 Pro Ser Pro Pro Gly Phe Thr Leu Pro Pro Leu Gly Gly Ser Leu Gly
 35 40 45
 Ala Gly Thr Ser Thr Xaa Arg Xaa Ser Glu Arg Thr Pro Gly Ala Ala
 50 55 60
 Thr Ala Ser Ala Ser Gly Ala Ala Glu Asp Gly Ala Cys Gly Cys Leu
 65 70 75 80
 Pro Asn Pro Gly Thr Phe Glu Glu Cys His Arg Lys Cys Lys Glu Leu
 85 90 95
 Phe Pro Ile Gln Met Glu Gly Val Lys Leu Thr Val Asn Lys Gly Leu
 100 105 110

Ser Asn His Phe Gln Val Asn His Thr Val Ala Leu Ser Thr Ile Gly
 115 120 125
 Glu Ser Asn Tyr His Phe Gly Val Thr Tyr Val Gly Thr Lys Gln Leu
 130 135 140
 Ser Pro Thr Glu Ala Phe Pro Val Leu Val Gly Asp Met Asp Asn Ser
 145 150 155 160
 Gly Ser Leu Asn Ala Gln Val Ile His Gln Leu Gly Pro Gly Leu Arg
 165 170 175
 Ser Lys Met Ala Ile Gln Thr Gln Gln Ser Lys Phe Val Asn Trp Gln
 180 185 190
 Val Asp Gly Glu Tyr Arg Gly Ser Asp Phe Thr Ala Ala Val Thr Leu
 195 200 205
 Gly Asn Pro Asp Val Leu Val Gly Ser Gly Ile Leu Val Ala His Tyr
 210 215 220
 Leu Gln Ser Ile Thr Pro Cys Leu Ala Leu Gly Gly Glu Leu Val Tyr
 225 230 235 240
 His Arg Arg Pro Gly Glu Glu Gly Thr Val Met Ser Leu Ala Gly Lys
 245 250 255
 Tyr Thr Leu Asn Asn Trp Leu Ala Thr Val Thr Leu Gly Gln Ala Gly
 260 265 270
 Met His Ala Thr Tyr Tyr His Lys Ala Ser Asp Gln Leu Gln Val Gly
 275 280 285
 Val Glu Phe Glu Ala Ser Thr Arg Xaa Gln Asp Thr Ser Val Ser Xaa
 290 295 300
 Xaa Val Pro Ala Trp Asn Leu Pro Lys Gly Gln Pro Xaa Leu Ser Lys
 305 310 315 320
 Xaa Leu Leu Gly

<210> 541

<211> 204

<212> PRT

<213> Homo sapiens

<400> 541

Arg Gly Pro Thr Phe Thr Pro Glu Ile Met Ala Ala Glu Asp Val Val
1 5 10 15
Ala Thr Gly Ala Asp Pro Ser Asp Leu Glu Ser Gly Gly Leu Leu His
20 25 30
Glu Ile Phe Thr Ser Pro Leu Asn Leu Leu Leu Gly Leu Cys Ile
35 40 45
Phe Leu Leu Tyr Lys Ile Val Arg Gly Asp Gln Pro Ala Ala Ser Gly
50 55 60
Asp Ser Asp Asp Asp Glu Pro Pro Pro Leu Pro Arg Leu Lys Arg Arg
65 70 75 80
Asp Phe Thr Pro Ala Glu Leu Arg Arg Phe Asp Gly Val Gln Asp Pro
85 90 95
Arg Ile Leu Met Ala Ile Asn Gly Lys Val Phe Asp Val Thr Lys Gly
100 105 110
Arg Lys Phe Tyr Gly Pro Glu Gly Pro Tyr Gly Val Phe Ala Gly Arg
115 120 125
Asp Ala Ser Arg Gly Leu Ala Thr Phe Cys Leu Asp Lys Glu Ala Leu
130 135 140
Lys Asp Glu Tyr Asp Asp Leu Ser Asp Leu Thr Ala Ala Gln Gln Glu
145 150 155 160
Thr Leu Ser Asp Trp Glu Ser Gln Phe Thr Phe Lys Tyr His His Val
165 170 175
Gly Lys Leu Leu Lys Glu Gly Glu Glu Pro Thr Val Tyr Ser Asp Glu
180 185 190
Glu Glu Pro Lys Asp Glu Ser Ala Arg Lys Asn Asp
195 200

<210> 542

<211> 193

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> {183}

<223> Xaa equals any of the naturally occurring L-amino acids

495

<400> 542

Pro Ala Tyr Ser Leu Gly Leu Leu Lys Ser Val Leu Asp Gly Gly Gly
 1 5 10 15

Ala Gly Ala His Gln Ala Arg Ser Asn Pro Ser Cys Met Tyr Pro Gln
 20 25 30

Gly Thr Phe Val Ile Pro Leu Leu Val Thr Ala His Arg Asp Pro Thr
 35 40 45

Gln Phe Lys Asp Pro Asp Cys Phe Asn Pro Thr Asn Phe Leu Asp Lys
 50 55 60

Gly Lys Phe Gln Gly Asn Asp Ala Phe Met Pro Phe Ala Ser Gly Ala
 65 70 75 80

Gly Arg Gly Gly Arg Gly Pro Ala Trp Thr Gly Ser Gly Val Pro Gly
 85 90 95

Ala His Cys Ala Pro Val Tyr Pro Ala Lys Gln Met Cys Leu Gly Thr
 100 105 110

Gly Leu Ala His Ser Gly Ile Phe Leu Phe Leu Thr Ala Thr Leu Gln
 115 120 125

Arg Phe Cys Leu Leu Pro Val Val Arg Pro Gly Thr Ile Asn Leu Thr
 130 135 140

Cys Ser Ala Leu Ala Trp Ala Val Ser Pro Gln Thr Ser Ser Ser Ser
 145 150 155 160

Gln Trp Pro Ala Glu Val Arg Leu His Tyr Gly Gly Leu Thr Gly Pro
 165 170 175

Gln Thr Ser Ile Pro Ser Xaa Val Asn Lys Gly Pro Lys Leu Gln Lys
 180 185 190

Lys

<210> 543

<211> 352

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (154)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (167)
 <223> xaa equals any of the naturally occurring L-amino acids

<400> 543
 Ser Thr Val Arg Xaa Pro Gly Arg Pro Thr Arg Pro Met Ala Ala Glu
 1 5 10 15
 Glu Pro Gln Gln Gln Lys Gln Glu Pro Leu Gly Ser Asp Ser Glu Val
 20 25 30
 Leu Thr Val Trp Pro Met Met Lys Pro Ser Trp Leu Ser Arg Thr Glu
 35 40 45
 Phe Ser Lys Arg Leu Leu Cys Arg Thr Leu Trp Cys Gln Ser Gly Trp
 50 55 60
 Ser Ser Arg Ser Tyr Thr Arg Ser Met Leu Lys Met Thr Thr Ser Ile
 65 70 75 80
 Asn Arg Arg Ser Arg Thr Ser Thr Lys Ser Thr Arg Thr Ser Ala Arg
 85 90 95
 Pro Gly Leu Thr Ala Thr Val Ser Ile Gly Leu Ser Asp Ser Pro Thr
 100 105 110
 Trp Arg His Cys Trp Met Thr Ala Arg Ser Cys Ser Gly Glu Lys Gly
 115 120 125
 Gly His Trp Ala Pro Arg Gln Val Gly Val Tyr Leu Leu Pro Gly Arg
 130 135 140
 Val Gly Cys Val Ser Ser Arg Val Ser Xaa Ser Phe Pro Gly Asp Gly
 145 150 155 160
 Leu Asp Ser Gly Leu Ala Xaa Arg Gly Ser Ala Val Ser Ala Leu Ala
 165 170 175
 Ser Gly Leu Val Glu Glu Pro Met Leu Gly Pro Pro Phe His Pro Thr
 180 185 190
 Pro Arg Phe Lys Ala Val Ser Ala Lys Ser Lys Glu Asp Leu Val Ser
 195 200 205

497

Gln Gly Phe Thr Glu Phe Thr Ile Glu Asp Phe His Asn Thr Phe Met
 210 215 220
 Asp Leu Ile Glu Gln Val Glu Lys Gln Thr Ser Val Ala Asp Leu Leu
 225 230 235 240
 Ala Ser Phe Asn Asp Gln Ser Thr Ser Asp Tyr Leu Val Val Tyr Leu
 245 250 255
 Arg Leu Leu Thr Ser Gly Tyr Leu Gln Arg Glu Ser Lys Phe Phe Glu
 260 265 270
 His Phe Ile Glu Gly Gly Arg Thr Val Lys Glu Phe Cys Gln Gln Glu
 275 280 285
 Val Glu Pro Met Cys Lys Glu Ser Asp His Ile His Ile Ile Ala Leu
 290 295 300
 Ala Gln Ala Leu Ser Val Ser Ile Gln Val Glu Tyr Met Asp Arg Gly
 305 310 315 320
 Glu Gly Gly Thr Thr Asn Pro His Ile Phe Pro Glu Gly Ser Glu Pro
 325 330 335
 Lys Val Tyr Leu Leu Tyr Arg Pro Gly His Tyr Asp Ile Leu Tyr Lys
 340 345 350

<210> 544

<211> 240

<212> PRT

<213> Homo sapiens

<400> 544

Ser Thr His Ala Ser Glu Met Ala Glu Arg Gly Tyr Ser Phe Ser Leu
 1 5 10 15
 Thr Thr Phe Ser Pro Ser Gly Lys Leu Val Gln Ile Glu Tyr Ala Leu
 20 25 30
 Ala Ala Val Ala Gly Gly Ala Pro Ser Val Gly Ile Lys Ala Ala Asn
 35 40 45
 Gly Val Val Leu Ala Thr Glu Lys Lys Gln Lys Ser Ile Leu Tyr Asp
 50 55 60
 Glu Arg Ser Val His Lys Val Glu Pro Ile Thr Lys His Ile Gly Leu

<213> Homo sapiens

Arg Cys Ile Leu Tyr Thr Gly Phe Met Leu Gly Ala Gln Arg Glu Val
1 5 10 15

Asp Ser Arg Leu Leu Ala Leu Pro Gly Arg Lys Val Pro Thr Ser Trp
20 25 30

Trp Asp Asp Leu Phe Lys Gly Ala Lys Glu His Gly Ala Val Ala Val
35 40 45

499

Glu Arg Val Thr Lys Ser Pro Gly Glu Thr Ser Lys Pro Arg Pro Phe
 50 55 60
 Ala Gly Gly Gly Tyr Arg Leu Gly Ala Ala Pro Glu Glu Glu Ser Ala
 65 70 75 80
 Tyr Val Ala Gly Glu Lys Arg Gln His Ser Ser Gln Asp Val His Val
 85 90 95
 Val Leu Lys Leu Trp Lys Ser Gly Phe Ser Leu Asp Asn Gly Glu Leu
 100 105 110
 Arg Ser Tyr Gln Asp Pro Ser Asn Ala Gln Phe Leu Glu Ser Ile Arg
 115 120 125
 Arg Gly Glu Val Pro Ala Glu Leu Arg Arg Leu Ala His Gly Gly Gln
 130 135 140
 Val Asn Leu Asp Met Glu Asp His Arg Asp Glu Asp Phe Val Lys Pro
 145 150 155 160
 Lys Gly Ala Phe Lys Ala Phe Thr Gly Glu Gly Gln Lys Leu Gly Ser
 165 170 175
 Thr Ala Pro Arg Cys
 180

<210> 546
 <211> 197
 <212> PRT
 <213> Homo sapiens

<400> 546
 Pro Arg Val Arg Arg Arg Ala Arg Ala Ala Gly Ser Ser His Ala
 1 5 10 15
 Ala Met Ala Asp Ser Glu Leu Gln Leu Val Glu Gln Arg Ile Arg Ser
 20 25 30
 Phe Pro Asp Phe Pro Thr Pro Gly Val Val Phe Arg Asp Ile Ser Pro
 35 40 45
 Val Leu Lys Asp Pro Ala Ser Phe Arg Ala Ala Ile Gly Leu Leu Ala
 50 55 60
 Arg His Leu Lys Ala Thr His Gly Gly Arg Ile Asp Tyr Ile Ala Gly
 65 70 75 80

500

Leu Asp Ser Arg Gly Phe Leu Phe Gly Pro Ser Leu Ala Gln Glu Leu
 85 90 95
 Gly Leu Gly Cys Val Leu Ile Arg Lys Arg Gly Lys Leu Pro Gly Pro
 100 105 110
 Thr Leu Trp Ala Ser Tyr Ser Leu Glu Tyr Gly Lys Ala Glu Leu Glu
 115 120 125
 Ile Gln Lys Asp Ala Leu Glu Pro Gly Gln Arg Val Val Val Val Asp
 130 135 140
 Asp Leu Leu Ala Thr Gly Gly Thr Met Asn Ala Ala Cys Glu Leu Leu
 145 150 155 160
 Gly Arg Leu Gln Ala Glu Val Leu Glu Cys Val Ser Leu Val Glu Leu
 165 170 175
 Thr Ser Leu Lys Gly Arg Glu Lys Leu Ala Pro Val Pro Phe Phe Ser
 180 185 190
 Leu Leu Gln Tyr Glu
 195

<210> 547

<211> 93

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 547

Glu Thr Gly Lys Glu Ser Lys Ala Leu Phe Leu Pro Phe Pro Gly Ser
 1 5 10 15
 Val Tyr Ser Thr Ser Thr Gly Glu Ala Ser Gly Glu Gly Leu Ser Pro
 20 25 30
 Leu Pro His Leu His Glu Phe Trp Asn Ser Val Leu Leu Ala Ala Cys
 35 40 45
 Phe Gln Leu Pro Pro Ile Ser Ile Ala Ala Gly Ser Ser Cys Leu Phe
 50 55 60
 Tyr Ser Val Ile Lys His Pro Ala Pro Thr Leu Ser Gln Arg Ser Ile
 65 70 75 80

501

Leu Ile Leu Xaa Lys Lys Ile Tyr Glu Glu Lys Lys Lys
 85 90

<210> 548

<211> 49

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (5)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 548

Gly Leu Gln Leu Xaa Ala His Ala Ala Gly Arg Val Pro Gly Cys Ala
 1 5 10 15

Leu Gln Gly Leu Gly His Phe Leu Gln Glu Asn Lys Gln Leu Leu Arg
 20 25 30

Asp Val Leu Ala Gln Glu Leu His Lys Pro Ala Phe Glu Gly Arg His
 35 40 45

Ile

<210> 549

<211> 379

<212> PRT

<213> Homo sapiens

<400> 549

Val Ala Cys Cys Val Arg Ile Pro Gly Pro Pro Arg Arg Ser Gly Pro
 1 5 10 15

Ala Met Ala Val Thr Ile Thr Leu Lys Thr Leu Gln Gln Gln Thr Phe
 20 25 30

Lys Ile Arg Met Glu Pro Asp Glu Thr Val Lys Val Leu Lys Glu Lys
 35 40 45

Ile Glu Ala Glu Lys Gly Arg Asp Ala Phe Pro Val Ala Gly Gln Lys
 50 55 60

Leu Ile Tyr Ala Gly Lys Ile Leu Ser Asp Asp Val Pro Ile Arg Asp
 65 70 75 80

Tyr Arg Ile Asp Glu Lys Asn Phe Val Val Val Met Val Thr Lys Thr
85 90 95

Lys Ala Gly Gln Gly Thr Ser Ala Pro Pro Glu Ala Ser Pro Thr Ala
100 105 110

Ala Pro Glu Ser Ser Thr Ser Phe Pro Pro Ala Pro Thr Ser Gly Met
115 120 125

Ser His Pro Pro Pro Ala Ala Arg Glu Asp Lys Ser Pro Ser Glu Glu
130 135 140

Ser Ala Pro Thr Thr Ser Pro Glu Ser Val Ser Gly Ser Val Pro Ser
145 150 155 160

Ser Gly Ser Ser Gly Arg Glu Glu Asp Ala Ala Ser Thr Leu Val Thr
165 170 175

Gly Ser Glu Tyr Glu Thr Met Leu Thr Glu Ile Met Ser Met Gly Tyr
180 185 190

Glu Arg Glu Arg Val Val Ala Ala Leu Arg Ala Ser Tyr Asn Asn Pro
195 200 205

His Arg Ala Val Glu Tyr Leu Leu Thr Gly Ile Pro Gly Ser Pro Glu
210 215 220

Pro Glu His Gly Ser Val Gln Glu Ser Gln Val Ser Glu Gln Pro Ala
225 230 235 240

Thr Glu Ala Gly Glu Asn Pro Leu Glu Phe Leu Arg Asp Gln Pro Gln
245 250 255

Phe Gln Asn Met Arg Gln Val Ile Gln Gln Asn Pro Ala Leu Leu Pro
260 265 270

Ala Leu Leu Gln Gln Leu Gly Gln Glu Asn Pro Gln Leu Leu Gln Gln
275 280 285

Ile Ser Arg His Gln Glu Gln Phe Ile Gln Met Leu Asn Glu Pro Pro
290 295 300

Gly Glu Leu Ala Asp Ile Ser Asp Val Glu Gly Glu Val Gly Ala Ile
305 310 315 320

Gly Glu Glu Ala Pro Gln Met Asn Tyr Ile Gln Val Thr Pro Gln Glu
325 330 335

Lys Glu Ala Ile Glu Arg Leu Lys Ala Leu Gly Phe Pro Glu Ser Leu
340 345 350

Val Ile Gln Ala Tyr Phe Ala Cys Glu Lys Asn Glu Asn Leu Ala Ala
355 360 365

Asn Phe Leu Leu Ser Gln Asn Phe Asp Asp Glu
370 375

<210> 550

<211> 275

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (260)

<223> Xaa equals any of the naturally occurring L-amino acids.

<220>

<221> SITE

<222> (261)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (267)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (272)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 550

Cys Ser Cys Lys Arg Xaa His Gln Gln Gln Val Leu Pro Pro Arg Gln
1 5 10 15

Pro Ser Ala Leu Val Pro Ser Val Thr Glu Tyr Arg Leu Asp Gly His
20 25 30

Thr Ile Ser Asp Leu Ser Arg Ser Ser Arg Gly Glu Leu Ile Pro Ile
 35 40 45
 Ser Pro Ser Thr Glu Val Gly Gly Ser Gly Ile Gly Thr Pro Pro Ser
 50 55 60
 Val Leu Lys Arg Gln Arg Lys Arg Arg Val Ala Leu Ser Pro Val Thr
 65 70 75 80
 Glu Asn Ser Thr Ser Leu Ser Phe Leu Asp Ser Cys Asn Ser Leu Thr
 85 90 95
 Pro Lys Ser Thr Pro Val Lys Thr Leu Pro Phe Ser Pro Ser Gln Phe
 100 105 110
 Leu Asn Phe Trp Asn Lys Gln Asp Thr Leu Glu Leu Glu Ser Pro Ser
 115 120 125
 Leu Thr Ser Thr Pro Val Cys Ser Gln Lys Val Val Val Thr Thr Pro
 130 135 140
 Leu His Arg Asp Lys Thr Pro Leu His Gln Lys His Ala Ala Phe Val
 145 150 155 160
 Thr Pro Asp Gln Lys Tyr Ser Met Asp Asn Thr Pro His Thr Pro Thr
 165 170 175
 Pro Phe Lys Asn Ala Leu Glu Lys Tyr Gly Pro Leu Lys Pro Leu Pro
 180 185 190
 Gln Thr Pro His Leu Glu Glu Asp Leu Lys Glu Val Leu Arg Ser Glu
 195 200 205
 Ala Gly Ile Glu Leu Ile Ile Glu Asp Asp Ile Arg Pro Glu Lys Gln
 210 215 220
 Lys Arg Lys Pro Gly Leu Arg Arg Ser Pro Xaa Lys Lys Val Arg Lys
 225 230 235 240
 Ser Leu Ala Leu Asp Ile Val Asp Glu Asp Val Lys Leu Met Met Ser
 245 250 255
 Thr Leu Pro Xaa Xaa Leu Ser Leu Ala Thr Xaa Ala Pro Cys Lys Xaa
 260 265 270
 Phe Gln Pro
 275

505

<211> 161

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (158)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 551

Asn Leu Ala Ala Ser Gly Gly Gly Pro Gln Ser Val Ser Gly Thr
 1 5 10 15

Leu Leu Cys Glu Pro Val Leu Thr Met Phe Ala Thr Ser Gly Ala Val
 20 25 30

Ala Ala Gly Lys Pro Tyr Ser Cys Ser Glu Cys Gly Lys Ser Phe Cys
 35 40 45

Tyr Ser Ser Val Leu Leu Arg His Glu Arg Ala His Gly Gly Asp Gly
 50 55 60

Arg Phe Arg Cys Leu Glu Cys Gly Glu Arg Cys Ala Arg Ala Ala Asp
 65 70 75 80

Leu Arg Ala His Arg Arg Thr His Ala Gly Gln Thr Leu Tyr Ile Cys
 85 90 95

Ser Glu Cys Gly Gln Ser Phe Arg His Ser Gly Arg Leu Asp Leu His
 100 105 110

Leu Gly Ala His Arg Gln Arg Cys Arg Thr Cys Pro Cys Arg Thr Cys
 115 120 125

Gly Arg Arg Phe Pro His Leu Pro Ala Leu Leu Leu His Arg Arg Arg
 130 135 140

Gln His Leu Pro Glu Arg Pro Arg Arg Cys Pro Leu Cys Xaa Leu Arg
 145 150 155 160

Phe

<210> 552

<211> 405

<212> PRT

<213> Homo sapiens

<400> 552

Pro Arg Val Arg Arg Arg Ala Arg Gly Arg Arg Val Arg Pro Ala Gly
1 5 10 15
Gly Pro Val Arg Arg Gly Ala Ala Val Arg Gly Ala Leu Arg Gly Ala
20 25 30
Ser Leu Gly His Gly Ala Ala Ala Arg Ala Gly Arg Pro Leu Cys Val
35 40 45
Arg His Ser Glu Pro Val Cys Gly Ser Asp Ala Asn Thr Tyr Ala Asn
50 55 60
Leu Cys Gln Leu Arg Ala Ala Ser Arg Arg Ser Glu Arg Leu His Arg
65 70 75 80
Pro Pro Val Ile Val Leu Gln Arg Gly Ala Cys Gly Gln Gly Gln Glu
85 90 95
Asp Pro Asn Ser Leu Arg His Lys Tyr Asn Phe Ile Ala Asp Val Val
100 105 110
Glu Lys Ile Ala Pro Ala Val Val His Ile Glu Leu Phe Arg Lys Leu
115 120 125
Pro Phe Ser Lys Arg Glu Val Pro Val Ala Ser Gly Ser Gly Phe Ile
130 135 140
Val Ser Glu Asp Gly Leu Ile Val Thr Asn Ala His Val Val Thr Asn
145 150 155 160
Lys His Arg Val Lys Val Glu Leu Lys Asn Gly Ala Thr Tyr Glu Ala
165 170 175
Lys Ile Lys Asp Val Asp Glu Lys Ala Asp Ile Ala Leu Ile Lys Ile
180 185 190
Asp His Gln Gly Lys Leu Pro Val Leu Leu Leu Gly Arg Ser Ser Glu
195 200 205
Leu Arg Pro Gly Glu Phe Val Val Ala Ile Gly Ser Pro Phe Ser Leu
210 215 220
Gln Asn Thr Val Thr Thr Gly Ile Val Ser Thr Thr Gln Arg Gly Gly
225 230 235 240
Lys Glu Leu Gly Leu Arg Asn Ser Asp Met Asp Tyr Ile Gln Thr Asp
245 250 255
Ala Ile Ile Asn Tyr Gly Asn Ser Gly Gly Pro Leu Val Asn Leu Asp
260 265 270

Gly Glu Val Ile Gly Ile Asn Thr Leu Lys Val Thr Ala Gly Ile Ser
 275 280 285
 Phe Ala Ile Pro Ser Asp Lys Ile Lys Lys Phe Leu Thr Glu Ser His
 290 295 300
 Asp Arg Gln Ala Lys Gly Lys Ala Ile Thr Lys Lys Lys Tyr Ile Gly
 305 310 315 320
 Ile Arg Met Met Ser Leu Thr Ser Ser Lys Ala Lys Glu Leu Lys Asp
 325 330 335
 Arg His Arg Asp Phe Pro Asp Val Ile Ser Gly Ala Tyr Ile Ile Glu
 340 345 350
 Val Ile Pro Asp Thr Pro Ala Glu Ala Gly Gly Leu Lys Glu Asn Asp
 355 360 365
 Val Ile Ile Ser Ile Asn Gly Gln Ser Val Val Ser Ala Asn Asp Val
 370 375 380
 Ser Asp Val Ile Lys Arg Glu Ser Thr Leu Asn Met Val Val Arg Arg
 385 390 395 400
 Val Met Lys Ile Ser
 405

<210> 553
 <211> 107
 <212> PRT
 <213> Homo sapiens

<400> 553
 Ala Gln Glu Asn Glu Glu Met Glu Gln Pro Met Gln Asn Gly Glu Glu
 1 5 10 15
 Asp Arg Pro Leu Gly Gly Gly Glu Gly His Gln Pro Ala Gly Asn Arg
 20 25 30
 Arg Gly Gln Ala Arg Arg Leu Ala Pro Asn Phe Arg Trp Ala Ile Pro
 35 40 45
 Asn Arg Gln Ile Asn Asp Gly Met Gly Gly Asp Gly Asp Asp Met Glu
 50 55 60
 Ile Phe Met Glu Glu Met Arg Glu Ile Arg Arg Lys Leu Arg Glu Leu
 65 70 75 80
 Gln Leu Arg Asn Cys Leu Arg Ile Leu Met Gly Glu Leu Ser Asn His

508

85

90

95

His Asp His His Asp Glu Phe Cys Leu Met Pro
100 105

<210> 554

<211> 229

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (20)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 554

Gly Leu Ser Ala Glu Ser Thr Xaa Thr Ser Thr Met Pro Met Xaa Leu
1 5 10 15

Gly Tyr Trp Xaa Ile Arg Gly Leu Ala His Xaa Ile Arg Leu Leu Leu
20 25 30

Glu Tyr Thr Asp Ser Ser Tyr Glu Glu Lys Lys Tyr Thr Met Gly Asp
35 40 45

Ala Pro Asp Tyr Asp Arg Ser Gln Trp Leu Asn Glu Lys Phe Lys Leu
50 55 60

Gly Leu Asp Phe Pro Asn Leu Pro Tyr Leu Ile Asp Gly Xaa His Lys

[illegible]

<210> 555

<211> 106

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (59)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (60)

<223> xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (72)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (98)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 555

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asn | Val | Ile | Ser | Val | Asp | Pro | Asn | Asp | Gln | Lys | Lys | Thr | Ala | Cys | Tyr |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Ile | Asp | Val | Glu | Val | Asp | Asp | Thr | Leu | Lys | Thr | Gln | Met | Asn | Ser |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Leu | Leu | Ser | Thr | Ala | Ser | Gln | Gln | Glu | Ile | Ala | Thr | Leu | Asp | Asn |
| | 35 | | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Lys | Thr | Met | Thr | Asp | Val | Val | Gly | Asn | Gln | Xaa | Xaa | Ser | Ala | Glu | Leu |
| | 50 | | | | | 55 | | | | | | 60 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Ser | Thr | Ser | Ser | Pro | Gly | Xaa | Gly | Gly | Cys | Val | Pro | Ile | Leu | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | 80 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Gln | Gly | Ala | Ala | Glu | Thr | Thr | Arg | Ile | Arg | Ala | Ser | Pro | Gly | Asn |
| | | | 85 | | | | | 90 | | | | | | 95 | |

| | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Xaa | Tyr | Ile | Gly | Pro | Leu | Pro | Gln | Pro |
| | | 100 | | | | | | 105 | |

<210> 556

<211> 86

<212> PRT

<213> Homo sapiens

<400> 556

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Arg | Ala | Thr | Lys | Gln | Asn | Thr | Thr | Lys | Pro | Asn | His | Arg | Ile | Ile |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Asn | Pro | Thr | Phe | Tyr | Thr | Met | Pro | Gln | Phe | Pro | Ile | Thr | Leu | His |
| | | | 20 | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ser | Phe | Cys | Val | Gln | Leu | Asn | Cys | Asn | Cys | Phe | Leu | Tyr | Leu | Glu |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Val | Thr | Ile | Glu | Leu | Glu | Thr | Phe | Tyr | Ser | Gly | Arg | Leu | Gly | Ser |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Trp | Trp | Asp | Ser | Val | Gly | Glu | Arg | Glu | Glu | Gly | Glu | Val | Gly | Gly |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

65

70

75

80

Leu Leu Pro Phe Arg Thr
85

<210> 557

<211> 565

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (57)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (71)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (75)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (82)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (118)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (120)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (552)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 557

Ala Ser Leu Thr Gly Thr Gln Ala Leu Pro Pro Leu Phe Ser Leu Gly
1 5 10 15

Tyr His Gln Ser Arg Trp Asn Tyr Arg Asp Glu Ala Asp Val Leu Glu
 20 25 30
 Val Asp Gln Gly Phe Asp Asp His Asn Leu Pro Cys Asp Val Ile Trp
 35 40 45
 Leu Asp Ile Glu His Ala Asp Gly Xaa Arg Tyr Phe Thr Trp Asp Pro
 50 55 60
 Ser Arg Phe Pro Gln Pro Xaa Thr Met Leu Xaa Arg Leu Ala Ser Lys
 65 70 75 80
 Arg Xaa Lys Leu Val Ala Ile Val Asp Pro His Ile Lys Val Asp Ser
 85 90 95
 Gly Tyr Arg Val His Glu Glu Leu Arg Asn Leu Gly Leu Tyr Val Lys
 100 105 110
 Thr Arg Asp Gly Ser Xaa Tyr Xaa Gly Trp Cys Trp Pro Gly Ser Ala
 115 120 125
 Gly Tyr Pro Asp Phe Thr Asn Pro Thr Met Arg Ala Trp Trp Ala Asn
 130 135 140
 Met Phe Ser Tyr Asp Asn Tyr Glu Gly Ser Ala Pro Asn Leu Phe Val
 145 150 155 160
 Trp Asn Asp Met Asn Glu Pro Ser Val Phe Asn Gly Pro Glu Val Thr
 165 170 175
 Met Leu Lys Asp Ala Gln His Tyr Gly Gly Trp Glu His Arg Asp Val
 180 185 190
 His Asn Ile Tyr Gly Leu Tyr Val His Met Ala Thr Ala Asp Gly Leu
 195 200 205
 Arg Gln Arg Ser Gly Gly Met Glu Arg Pro Phe Val Leu Ala Arg Ala
 210 215 220
 Phe Phe Ala Gly Ser Gln Arg Phe Gly Ala Val Trp Thr Gly Asp Asn
 225 230 235 240
 Thr Ala Glu Trp Asp His Leu Lys Ile Ser Ile Pro Met Cys Leu Ser
 245 250 255
 Leu Gly Leu Val Gly Leu Ser Phe Cys Gly Ala Asp Val Gly Gly Phe
 260 265 270
 Phe Lys Asn Pro Glu Pro Glu Leu Leu Val Arg Trp Tyr Gln Met Gly
 275 280 285

Ala Tyr Gln Pro Phe Phe Arg Ala His Ala His Leu Asp Thr Gly Arg
290 295 300

Arg Glu Pro Trp Leu Leu Pro Ser Gln His Asn Asp Ile Ile Arg Asp
305 310 315 320

Ala Leu Gly Gln Arg Tyr Ser Leu Leu Pro Phe Trp Tyr Thr Leu Leu
325 330 335

Tyr Gln Ala His Arg Glu Gly Ile Pro Val Met Arg Pro Leu Trp Val
340 345 350

Gln Tyr Pro Gln Asp Val Thr Thr Phe Asn Ile Asp Asp Gln Tyr Leu
355 360 365

Leu Gly Asp Ala Leu Leu Val His Pro Val Ser Asp Ser Gly Ala His
370 375 380

Gly Val Gln Val Tyr Leu Pro Gly Gln Gly Glu Val Trp Tyr Asp Ile
385 390 395 400

Gln Ser Tyr Gln Lys His His Gly Pro Gln Thr Leu Tyr Leu Pro Val
405 410 415

Thr Leu Ser Ser Ile Pro Val Phe Gln Arg Gly Gly Thr Ile Val Pro
420 425 430

Arg Trp Met Arg Val Arg Arg Ser Ser Glu Cys Met Lys Asp Asp Pro
435 440 445

Ile Thr Leu Phe Val Ala Leu Ser Pro Gln Gly Thr Ala Gln Gly Glu
450 455 460

Leu Phe Leu Asp Asp Gly His Thr Phe Asn Tyr Gln Thr Arg Gln Glu
465 470 475 480

Phe Leu Leu Arg Arg Phe Ser Phe Ser Gly Asn Thr Leu Val Ser Ser
485 490 495

Ser Ala Asp Pro Glu Gly His Phe Glu Thr Pro Ile Trp Ile Glu Arg
500 505 510

Val Val Ile Ile Gly Ala Gly Lys Pro Ala Ala Val Val Leu Gln Thr
515 520 525

Lys Gly Ser Pro Glu Ser Arg Leu Ser Phe Gln His Asp Pro Glu Thr
530 535 540

Ser Val Leu Val Leu Arg Lys Xaa Gly Ile Asn Val Ala Ser Asp Trp
545 550 555 560

Ser Ile His Leu Arg
565

<210> 558

<211> 160

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (39)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 558

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Glu | Ala | Val | Leu | Pro | Gln | Ala | Val | Leu | Arg | His | Pro | Val | Arg | Thr |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Gln | Arg | Arg | Glu | His | Arg | Gly | Arg | Gly | Leu | Leu | His | Leu | Arg | Glu | Ala |
| | 20 | | | | | 25 | | | | | | | 30 | | |
| Pro | Gly | Gly | Gly | Ala | Ala | Xaa | His | Arg | Pro | His | Arg | Gly | Pro | Arg | Gly |
| | 35 | | | | | 40 | | | | | | 45 | | | |
| Pro | Ser | Arg | Gly | Ala | Glu | Gly | Glu | Arg | Pro | Pro | Glu | Gly | Pro | Ser | Arg |
| | 50 | | | | 55 | | | | | | 60 | | | | |
| Ala | Ser | Ser | Val | Thr | Thr | Phe | Thr | Gly | Glu | Pro | Asn | Thr | Cys | Pro | Arg |
| 65 | | | | 70 | | | | | 75 | | | | | 80 | |
| Cys | Ser | Lys | Lys | Val | Tyr | Phe | Ala | Glu | Lys | Val | Thr | Ser | Leu | Gly | Lys |
| | | | 85 | | | | | | 90 | | | | | 95 | |
| Asp | Trp | His | Arg | Pro | Cys | Leu | Arg | Cys | Glu | Arg | Cys | Gly | Lys | Thr | Leu |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Thr | Pro | Gly | Gly | His | Ala | Glu | His | Asp | Gly | Gln | Pro | Tyr | Cys | His | Lys |
| | 115 | | | | | | 120 | | | | | 125 | | | |
| Pro | Cys | Tyr | Gly | Ile | Leu | Phe | Gly | Pro | Lys | Gly | Val | Asn | Thr | Gly | Ala |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Val | Gly | Ser | Tyr | Ile | Tyr | Asp | Arg | Asp | Pro | Glu | Gly | Lys | Val | Gln | Pro |
| 145 | | | | | 150 | | | | | 155 | | | | 160 | |

<210> 559

<211> 480

<212> PRT

<213> Homo sapiens

<400> 559

Gly Cys Ile Gly Tyr Leu Val Leu Leu Trp Pro Leu Pro Leu Ile His
 1 5 10 15

Phe Gly Leu Ala Asn Gln Ser Glu Asp Leu Ser Val Phe Tyr Pro Gly
 20 25 30

Thr Leu Leu Glu Thr Gly His Asp Ile Leu Phe Phe Trp Val Ala Arg
 35 40 45

Met Val Met Leu Gly Leu Lys Leu Thr Gly Arg Leu Pro Phe Arg Glu
 50 55 60

Val Tyr Leu His Ala Ile Val Arg Asp Ala His Gly Arg Lys Met Ser
 65 70 75 80

Lys Ser Leu Gly Asn Val Ile Asp Pro Leu Asp Val Ile Tyr Gly Ile
 85 90 95

Ser Leu Gln Gly Leu His Asn Gln Leu Leu Asn Ser Asn Leu Asp Pro
 100 105 110

Ser Glu Val Glu Lys Ala Lys Glu Gly Gln Lys Ala Asp Phe Pro Ala
 115 120 125

Gly Ile Pro Glu Cys Gly Thr Asp Ala Leu Arg Phe Gly Leu Cys Ala
 130 135 140

Tyr Met Ser Gln Gly Arg Asp Ile Asn Leu Asp Val Asn Arg Ile Leu
 145 150 155 160

Gly Tyr Arg His Phe Cys Asn Lys Leu Trp Asn Ala Thr Lys Phe Ala
 165 170 175

Leu Arg Gly Leu Gly Lys Gly Phe Val Pro Ser Pro Thr Ser Gln Pro
 180 185 190

Gly Gly His Glu Ser Leu Val Asp Arg Trp Ile Arg Ser Arg Leu Thr
 195 200 205

Glu Ala Val Arg Leu Ser Asn Gln Gly Phe Gln Ala Tyr Asp Phe Pro
 210 215 220

Ala Val Thr Thr Ala Gln Tyr Ser Phe Trp Leu Tyr Glu Leu Cys Asp
 225 230 235 240

516

Val Tyr Leu Glu Cys Leu Lys Pro Val Leu Asn Gly Val Asp Gln Val
245 250 255

Ala Ala Glu Cys Ala Arg Gln Thr Leu Tyr Thr Cys Leu Asp Val Gly
260 265 270

Leu Arg Leu Leu Ser Pro Phe Met Pro Phe Val Thr Glu Glu Leu Phe
275 280 285

Gln Arg Leu Pro Arg Arg Met Pro Gln Ala Pro Pro Ser Leu Cys Val
290 295 300

Thr Pro Tyr Pro Glu Pro Ser Glu Cys Ser Trp Lys Asp Pro Glu Ala
305 310 315 320

Glu Ala Ala Leu Glu Leu Ala Leu Ser Ile Thr Arg Ala Val Arg Ser
325 330 335

Leu Arg Ala Asp Tyr Asn Leu Thr Arg Ile Arg Pro Asp Cys Phe Leu
340 345 350

Glu Val Ala Asp Glu Ala Thr Gly Ala Leu Ala Ser Ala Val Ser Gly
355 360 365

Tyr Val Gln Ala Leu Ala Ser Ala Gly Val Val Ala Val Leu Ala Leu
370 375 380

Gly Ala Pro Ala Pro Gln Gly Cys Ala Val Ala Leu Ala Ser Asp Arg
385 390 395 400

Cys Ser Ile His Leu Gln Leu Gln Gly Leu Val Asp Pro Ala Arg Glu
405 410 415

Leu Gly Lys Leu Gln Ala Lys Arg Val Glu Ala Gln Arg Gln Ala Gln
420 425 430

Arg Leu Arg Glu Arg Arg Ala Ala Ser Gly Tyr Pro Val Lys Val Pro
435 440 445

Leu Glu Val Gln Glu Ala Asp Glu Ala Lys Leu Gln Gln Thr Glu Ala
450 455 460

Glu Leu Arg Lys Val Asp Glu Ala Ile Ala Leu Phe Gln Lys Met Leu
465 470 475 480

<210> 560

517

<211> 96

<212> PRT

<213> Homo sapiens

<400> 560

Ala Cys Leu Glu Arg Cys Gly Ser Trp Arg Pro His Arg Pro Met Thr
1 5 10 15

Ser Gly Ala Arg Glu Asn Pro Ile Gln Val Pro Arg Ser Ser Leu Glu
20 25 30

Ala Thr Gly Ala Gln Glu Arg Trp Ala Glu Asp Val Pro Tyr Pro Thr
35 40 45

Thr Arg Ala Val Ser Leu Pro Pro Ser Leu Gly Val Gly Ser Thr Gly
50 55 60

Met Ser Ser Ser Arg Phe Leu Gly Ser Leu Gly Lys His Gly Arg Leu
65 70 75 80

Asp Ser Ser Arg Arg Ala Arg Leu Trp Gly Arg Gly Gly Arg Gly Gly
85 90 95

<210> 561

<211> 60

<212> PRT

<213> Homo sapiens

<400> 561

Ile Arg His Glu Ser Ser Ile Leu Ser Val Leu Phe Ile Arg Phe Leu
1 5 10 15

Lys Cys Ala Asp Pro Phe Lys Thr Pro Ala Tyr Leu Cys Asn Lys Glu
20 25 30

Lys Tyr Ser Lys Ile Leu Pro Ser Phe Ser His Thr Val Leu Lys Met
35 40 45

Leu Gln Asp Gln Ile Ile Ala His Lys Ile Arg Ser
50 55 60

<210> 562

<211> 241

<212> PRT

<213> Homo sapiens

<400> 562

Ser Ser Met Ala Lys Pro Cys Gly Val Arg Leu Ser Gly Glu Ala Arg
1 5 10 15

Lys Gln Val Glu Val Phe Arg Gln Asn Leu Phe Gln Glu Ala Glu Glu
20 25 30

Phe Leu Tyr Arg Phe Leu Pro Gln Lys Ile Ile Tyr Leu Asn Gln Leu
35 40 45

Leu Gln Glu Asp Ser Leu Asn Val Ala Asp Leu Thr Ser Leu Arg Ala
50 55 60

Pro Leu Asp Ile Pro Ile Pro Asp Pro Pro Pro Lys Asp Asp Glu Met
65 70 75 80

Glu Thr Asp Lys Gln Glu Lys Lys Glu Val Pro Lys Cys Gly Phe Leu
85 90 95

Pro Gly Asn Glu Lys Val Leu Ser Leu Leu Ala Leu Val Lys Pro Glu
100 105 110

Val Trp Thr Leu Lys Glu Lys Cys Ile Leu Val Ile Thr Trp Ile Gln
115 120 125

His Leu Ile Pro Lys Ile Glu Asp Gly Asn Asp Phe Gly Val Ala Ile
130 135 140

Gln Glu Lys Val Leu Glu Arg Val Asn Ala Val Lys Thr Lys Val Glu
145 150 155 160

Ala Phe Gln Thr Thr Ile Ser Lys Tyr Phe Ser Glu Arg Gly Asp Ala
165 170 175

Val Ala Lys Ala Ser Lys Glu Thr His Val Met Asp Tyr Arg Ala Leu
180 185 190

Val His Glu Arg Asp Glu Ala Ala Tyr Gly Glu Leu Arg Ala Met Val
195 200 205

Leu Asp Leu Arg Ala Phe Tyr Ala Glu Leu Tyr His Ile Ile Ser Ser
210 215 220

Asn Leu Glu Lys Ile Val Asn Pro Lys Gly Glu Glu Lys Pro Ser Met
225 230 235 240

Tyr

```
<220>  
<221> SITE  
<222> (145)  
<223> Xaa equals any of the naturally occurring L-amino acids
```

Leu Gly Ser Ile Gln Val Met Gln Ala Val Arg Asn Ala Gly Ser Arg
1 5 10 15

Phe Leu Arg Ser Trp Thr Trp Pro Gln Thr Ala Gly Arg Val Val Ala
20 25 30

Arg Thr Pro Ala Gly Thr Ile Cys Thr Gly Ala Arg Gln Leu Gln Asp
35 40 45

Ala Ala Ala Lys Gln Lys Val Glu Gln Asn Ala Ala Pro Ser His Thr
50 55 60

Lys Phe Ser Ile Tyr Pro Pro Ile Pro Gly Glu Glu Ser Ser Leu Arg
65 70 75 80

Trp Ala Gly Lys Lys Phe Glu Glu Ile Pro Ile Ala His Ile Lys Ala
85 90 95

Ser His Asn Asn Thr Gln Ile Gln Val Val Ser Ala Ser Asn Glu Pro
100 105 110

Leu Ala Phe Ala Ser Cys Gly Thr Glu Gly Phe Arg Asn Ala Lys Lys
115 120 125

Gly Thr Gly Ile Ala Ala Gln Thr Ala Gly Ile Ala Ala Ala Ala Arg
130 135 140

Xaa Lys Gln Lys Gly Val Ile His Ile Arg Val Val Val Lys Gly Leu
145 150 155 160

Gly Pro Gly Arg Leu Ser Ala Met His Gly Leu Ile Met Gly Gly Leu
165 170 175

Glu Val Ile Ser Ile Thr Asp Asn Thr Pro Ile Pro His Asn Gly Cys
180 185 190

Arg Pro Arg Lys Ala Arg Lys Leu
195 200

<210> 564
<211> 115
<212> PRT
<213> Homo sapiens

<400> 564
Val Arg Leu Val Pro Gly Ala Asp Lys Tyr Asn Asp Asp Ile Arg Lys
1 5 10 15
Gly Ile Val Leu Leu Glu Glu Leu Leu Pro Lys Gly Ser Lys Glu Glu
20 25 30
Gln Arg Asp Tyr Val Phe Tyr Leu Ala Val Gly Asn Tyr Arg Leu Lys
35 40 45
Glu Tyr Glu Lys Ala Leu Lys Tyr Val Arg Gly Leu Leu Gln Thr Glu
50 55 60
Pro Gln Asn Asn Gln Ala Lys Glu Leu Glu Arg Leu Ile Asp Lys Ala
65 70 75 80
Met Lys Lys Asp Gly Leu Val Gly Met Ala Ile Val Gly Gly Met Ala
85 90 95
Leu Gly Val Ala Gly Leu Ala Gly Leu Ile Gly Leu Ala Val Ser Lys
100 105 110
Ser Lys Ser
115

<210> 565
<211> 101
<212> PRT
<213> Homo sapiens

<400> 565
Pro Thr Arg Pro Asp Glu His Asp Glu Asn Asn Ala Glu Ala Ser Ala
1 5 10 15
Glu Leu Ser Asn Glu Gly Val Met Asn His Arg Ser Glu Glu Glu Arg
20 25 30
Val Thr Glu Thr Gln Lys Asn Glu Arg Val Lys Lys Gln Leu Gln Ala
35 40 45
Leu Ser Ser Glu Leu Ala Gln Ala Arg Asp Glu Thr Lys Lys Thr Gln

521

50 55 60
Asn Asp Val Leu His Ala Glu Asn Val Lys Ala Gly Arg Asp Lys Tyr
65 70 75 80
Lys Thr Leu Arg Gln Ile Arg Gln Gly Asn Thr Lys Gln Arg Ile Asp
85 90 95
Glu Phe Glu Ala Met
100

<210> 566
<211> 25
<212> PRT
<213> Homo sapiens

<400> 566
Thr Ala Asp Leu Val Ile Arg Pro Pro Arg Pro Leu Lys Val Leu Gly
1 5 10 15
Phe Cys Val Phe Cys Ala Pro Pro Leu
20 25

<210> 567
<211> 274
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (182)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (216)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (222)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (224)
<223> Xaa equals any of the naturally occurring L-amino acids

522

<220>

<221> SITE

<222> (228)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (231)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 567

Ala Ser Pro Glu Val Glu Ala Gly Ala Ala Arg Gln Pro Leu Leu Gly
1 5 10 15

Val Ala Gly Gly Gln Thr Leu Gly Ala Thr Pro Gly Pro Val Met Asn
20 25 30

Gly Pro Ala Asp Gly Glu Val Asp Tyr Lys Lys Lys Tyr Arg Asn Leu
35 40 45

Lys Arg Lys Leu Lys Phe Leu Ile Tyr Glu His Glu Cys Phe Gln Glu
50 55 60

Glu Leu Arg Lys Ala Gln Arg Lys Leu Leu Lys Val Ser Arg Asp Lys
65 70 75 80

Ser Phe Leu Leu Asp Arg Leu Leu Gln Tyr Glu Asn Val Asp Glu Asp
85 90 95

Ser Ser Asp Ser Asp Ala Thr Ala Ser Ser Asp Asn Ser Glu Thr Glu
100 105 110

Gly Thr Pro Lys Leu Ser Asp Thr Pro Ala Pro Lys Arg Lys Arg Ser
115 120 125

Pro Pro Leu Gly Gly Ala Pro Ser Pro Ser Ser Leu Ser Leu Pro Pro
130 135 140

Ser Thr Gly Phe Pro Leu Gln Ala Ser Gly Val Pro Ser Pro Tyr Leu
145 150 155 160

Ser Ser Leu Ala Ser Ser Arg Tyr Pro Pro Phe Pro Ser Asp Tyr Leu
165 170 175

Ala Leu Gln Leu Pro Xaa Pro Ser Pro Leu Arg Pro Lys Arg Glu Lys
180 185 190

Arg Pro Arg Leu Pro Arg Lys Leu Lys Met Ala Val Gly Pro Pro Asp
195 200 205

Cys Pro Val Gly Gly Pro Leu Xaa Phe Pro Gly Arg Gly Xaa Gly Xaa
 210 215 220

Gly Val Gly Xaa Thr Leu Xaa Pro Leu Pro Pro Pro Lys Met Pro Pro
 225 230 235 240

Pro Thr Ile Leu Ser Thr Val Pro Arg Gln Met Phe Ser Asp Ala Gly
 245 250 255

Ser Gly Asp Asp Ala Leu Asp Gly Asp Asp Asp Leu Val Ile Asp Ile
 260 265 270

Pro Glu

<210> 568

<211> 133

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (47)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 568

Ala Arg Gly Asp His Val Arg Ser Arg Glu Thr Gly Arg Gln Ser Ala
 1 5 10 15

Ser Lys Gly Gln Ile Pro Leu Leu Pro Arg Gly Pro Ala Val Pro Gly
 20 25 30

Gly Pro Ser Ala Gln Thr Ala Ala Gln Arg Glu Leu Arg Gly Xaa Val
 35 40 45

Gly Ala Gly Ala Pro Val Tyr Leu Ala Ala Val Leu Glu Tyr Leu Thr
 50 55 60

Ala Glu Ile Leu Glu Leu Ala Gly Asn Ala Ala Arg Asp Asn Lys Lys
 65 70 75 80

Thr Arg Ile Ile Pro Arg His Leu Gln Leu Ala Ile Arg Asn Asp Glu
 85 90 95

Glu Leu Asn Lys Leu Leu Gly Lys Val Thr Ile Ala Gln Gly Gly Val
 100 105 110

Leu Pro Asn Ile Gln Ala Val Leu Leu Pro Lys Lys Thr Glu Ser Gln
 115 120 125

Lys Thr Lys Ser Lys
130

<210> 569

<211> 153

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (136)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (137)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (152)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 569

Met Cys Arg Gly Tyr Ala Trp Asn Pro Gly Ile Thr Leu Gln Asn Arg
1 5 10 15

Lys Thr Lys Glu Gly Pro Arg Ala Pro Pro Ser Arg Met Pro Glu Pro
20 25 30

Ala Gly Gly Leu Arg Gly Cys Glu Ala Val Gly Thr Leu Leu Met Lys
35 40 45

Glu Thr Val Phe Ala Leu His Pro Ser Leu Pro Leu Gly Ala Gly Ser
50 55 60

Ser Pro Ser Ala Thr Cys Ser Glu Gly Leu His Leu Arg Gly Glu Gly
65 70 75 80

Trp Gly Lys Ser Pro Pro Val Pro Phe Leu Trp Pro Cys Cys Pro His
85 90 95

Thr Gln Leu Arg Gly Pro Thr Leu Gly Lys Ala Gly Ser Ala Arg Ser
100 105 110

Leu Ser Pro Ile Ser Ala Leu Ser Ala Trp Ile Pro Ala Glu Ala Met
115 120 125

Lys Gly Asn Lys Glu Lys Arg Xaa Xaa Lys Lys Lys Lys Lys Lys Lys
 130 135 140

Lys Lys Lys Lys Lys Lys Lys Xaa Pro
 145 150

<210> 570

<211> 327

<212> PRT

<213> Homo sapiens

<400> 570

Pro Gly Ser Pro Arg Arg Cys Asp Ile Ile Ile Ile Ser Gly Arg Lys
 1 5 10 15

Glu Lys Cys Glu Ala Ala Lys Glu Ala Leu Glu Ala Leu Val Pro Val
 20 25 30

Thr Ile Glu Val Glu Val Pro Phe Asp Leu His Arg Tyr Val Ile Gly
 35 40 45

Gln Lys Gly Ser Gly Ile Arg Lys Met Met Asp Glu Phe Glu Val Asn
 50 55 60

Ile His Val Pro Ala Pro Glu Leu Gln Ser Asp Ile Ile Ala Ile Thr
 65 70 75 80

Gly Leu Ala Ala Asn Leu Asp Arg Ala Lys Ala Gly Leu Leu Glu Arg
 85 90 95

Val Lys Glu Leu Gln Ala Glu Gln Glu Asp Arg Ala Leu Arg Ser Phe
 100 105 110

Lys Leu Ser Val Thr Val Asp Pro Lys Tyr His Pro Lys Ile Ile Gly
 115 120 125

Arg Lys Gly Ala Val Ile Thr Gln Ile Arg Leu Glu His Asp Val Asn
 130 135 140

Ile Gln Phe Pro Asp Lys Asp Asp Gly Asn Gln Pro Gln Asp Gln Ile
 145 150 155 160

Thr Ile Thr Gly Tyr Glu Lys Asn Thr Glu Ala Ala Arg Asp Ala Ile
 165 170 175

Leu Arg Ile Val Gly Glu Leu Glu Gln Met Val Ser Glu Asp Val Pro
 180 185 190

Leu Asp His Arg Val His Ala Arg Ile Ile Gly Ala Arg Gly Lys Ala

195 200 205
 Ile Arg Lys Ile Met Asp Glu Phe Lys Val Asp Ile Arg Phe Pro Gln
 210 215 220
 Ser Gly Ala Pro Asp Pro Asn Cys Val Thr Val Thr Gly Leu Pro Glu
 225 230 235 240
 Asn Val Glu Glu Ala Ile Asp His Ile Leu Asn Leu Glu Glu Glu Tyr
 245 250 255
 Leu Ala Asp Val Val Asp Ser Glu Ala Leu Gln Val Tyr Met Lys Pro
 260 265 270
 Pro Ala His Glu Glu Ala Lys Ala Pro Ser Arg Gly Phe Val Val Arg
 275 280 285
 Asp Ala Pro Trp Thr Ala Ser Ser Ser Glu Lys Ala Pro Asp Met Ser
 290 295 300
 Ser Ser Glu Glu Phe Pro Ser Phe Gly Ala Gln Val Ala Pro Lys Thr
 305 310 315 320
 Leu Pro Trp Gly Pro Lys Arg
 325

<210> 571
 <211> 166
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (9)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (12)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 571
 Gly Asn Ser Arg Val Asp Pro Arg Xaa Arg Gly Xaa Ala His Thr Cys
 1 5 10 15
 Ala Pro Cys Pro Ala Pro Gly Pro Leu Ala Gly Arg Ala Val Ser Gly
 20 25 30
 His Gly Ser Leu Pro Pro Asp Arg Arg Ala Pro Ser Ala Leu Ser Ser

527

35 40 45
 Pro Ala Asp Glu Gly Glu Arg Arg Arg Pro Asp Leu Asp Glu Ile His
 50 55 60
 Arg Glu Leu Arg Pro Gln Gly Ser Ala Arg Pro Gln Pro Asp Pro Asn
 65 70 75 80
 Ala Glu Phe Asp Pro Asp Leu Pro Gly Gly Gly Leu His Arg Cys Leu
 85 90 95
 Ala Cys Ala Arg Tyr Phe Ile Asp Ser Thr Asn Leu Lys Thr His Phe
 100 105 110
 Arg Ser Lys Asp His Lys Lys Arg Leu Lys Gln Leu Ser Val Glu Pro
 115 120 125
 Tyr Ser Gln Glu Glu Ala Glu Arg Ala Ala Gly Met Gly Ser Tyr Val
 130 135 140
 Pro Pro Arg Arg Leu Ala Val Pro Thr Glu Val Ser Thr Glu Val Pro
 145 150 155 160
 Glu Met Asp Thr Ser Thr
 165

<210> 572

<211> 113

<212> PRT

<213> Homo sapiens

<400> 572

Gln Ser Ser Thr Phe His Pro Ala Pro Ala Phe Gly Ala Thr Val Ala
 1 5 10 15
 Ala Phe His Arg Arg Ala Ala Leu Arg Ala Pro Glu Pro Ala Met Ser
 20 25 30
 Gly Pro Asn Gly Asp Leu Gly Met Pro Val Glu Ala Gly Ala Glu Gly
 35 40 45
 Glu Glu Asp Gly Phe Gly Glu Ala Glu Tyr Ala Ala Ile Asn Ser Met
 50 55 60
 Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys Asn Asp
 65 70 75 80
 His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg Gln Thr
 85 90 95

Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp Ala Ser
 100 105 110

Pro

<210> 573
 <211> 99
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (27)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (37)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (38)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 573
 Gly Ser Gly Ser Ser Arg Asp Leu His Lys Ala Leu Trp Glu Ala Gly
 1 5 10 15
 Trp Glu Thr Val Glu Gly Gly Cys Pro Leu Xaa Pro Arg Arg His Arg
 20 25 30
 Ile Trp Ala Leu Xaa Xaa Ala Phe Leu Pro Glu Tyr Ala Ala Ile Asn
 35 40 45
 Ser Met Leu Asp Gln Ile Asn Ser Cys Leu Asp His Leu Glu Glu Lys
 50 55 60
 Asn Asp His Leu His Ala Arg Leu Gln Glu Leu Leu Glu Ser Asn Arg
 65 70 75 80
 Gln Thr Arg Leu Glu Phe Gln Gln Gln Leu Gly Glu Ala Pro Ser Asp
 85 90 95
 Ala Ser Pro

<210> 574
<211> 197
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (97)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (124)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (129)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 574
Arg Trp Ala Arg Val Glu Ala Ala Val Met Glu Gly Ala Gly Ala Gly
1 5 10 15
Ser Gly Phe Arg Lys Glu Leu Val Ser Arg Leu Leu His Leu His Phe
20 25 30
Lys Asp Asp Lys Thr Lys Val Ser Gly Asp Ala Leu Gln Leu Met Val
35 40 45
Glu Leu Leu Lys Val Phe Val Val Glu Ala Ala Val Arg Gly Val Arg
50 55 60
Gln Ala Gln Ala Glu Asp Ala Leu Arg Val Asp Val Asp Gln Leu Glu
65 70 75 80
Lys Val Leu Arg Ser Cys Ser Gly Leu Leu Gly Ile Ser Ala Val Ala
85 90 95
Xaa Ala Thr Pro Arg Gly Ala Pro Gly Pro Gln Lys Gln Ala Leu Cys
100 105 110
Phe Gln Arg Pro Leu Ile Arg Gly Arg Glu Gly Xaa Glu Gly Phe Gly
115 120 125
Xaa Asp Ser Asn Lys Ile Ser Gly Ser Leu Gln Pro Val Gln Lys Gly
130 135 140
Gln Asp Cys Ser Ala Leu Arg Ala Leu Glu Cys Pro Val Gly Thr Leu

145 150 155 160
Val Trp Glu Gly Ala Ala Pro Gly Glu Ser Leu Pro Leu Leu Pro Gly
 165 170 175
Thr Ile Val Cys Met Pro Pro Gly Val Leu Gln Ala Gly Ala Gly Lys
 180 185 190
Gly Leu Ala Ser Arg
 195

<210> 575
<211> 47
<212> PRT
<213> Homo sapiens

<400> 575
Leu Pro Met Val Asp Leu Met Glu Lys Leu Asn Ile Phe His Tyr Ala
1 5 10 15
Leu Gln Asn Thr Val Tyr Val Ser Ala Ser Leu Gly Asn Gly Arg Gly
 20 25 30
Gln Lys Lys Val Thr Phe Asn Leu Cys Ile Phe Ala Lys Pro Tyr
 35 40 45

<210> 576
<211> 115
<212> PRT
<213> Homo sapiens

<400> 576
Trp Ser Arg Thr Ser Gln Pro Leu Pro Ser Thr Val Gly Cys Pro Arg
1 5 10 15
Arg Arg Gly Phe Lys Asp Phe Gln Arg Arg Ile Leu Val Ala Thr Asn
 20 25 30
Leu Phe Gly Arg Gly Met Asp Ile Glu Arg Val Asn Ile Ala Phe Asn
 35 40 45
Tyr Asp Met Pro Glu Asp Ser Asp Thr Tyr Leu His Arg Val Ala Arg
 50 55 60
Ala Gly Arg Phe Gly Thr Lys Gly Leu Ala Ile Thr Phe Val Ser Asp
65 70 75 80

531

Glu Asn Asp Ala Lys Ile Leu Asn Asp Val Gln Asp Arg Phe Glu Val
85 90 95

Asn Ile Ser Glu Leu Pro Asp Glu Ile Asp Ile Ser Ser Tyr Ile Glu
100 105 110

Gln Thr Arg
115

<210> 577

<211> 346

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (37)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 577

Val Thr Ser Cys Val Ala Leu Leu Pro Ala Arg Arg Met Thr Tyr Thr
1 5 10 15

Thr Glu Thr Ala Leu Leu Asn Trp Ser Thr Cys Gln Met Val Leu Arg
20 25 30

Gly Ala Glu Thr Xaa Gly Cys Val Ile Val Ser Ala Ala Lys Ala Gln
35 40 45

Leu Leu Gln Cys Gln His His Pro Ala Trp Tyr Gly Asp Thr Leu Lys
50 55 60

Gln Lys Thr Ser Trp Thr Cys Leu Leu Asp Gly Met Gln Tyr Phe Ala
65 70 75 80

Thr Thr Glu Ser Ser Pro Thr Glu Gln Asp Gly Arg Gln Leu Trp Leu
85 90 95

Glu Val Lys Asn Ile Glu Glu His Arg Gln Arg Ser Leu Asp Ser Val
100 105 110

Gln Glu Leu Met Glu Ser Gly Gln Ala Val Gly Gly Met Val Thr Thr
115 120 125

Thr Thr Asp Trp Asn Gln Pro Ala Glu Ala Gln Gln Ala Gln Gln Val
130 135 140

Gln Arg Ile Ile Ser Arg Cys Asn Cys Arg Met Tyr Tyr Ile Ser Tyr
145 150 155 160

Ser His Asp Ile Asp Pro Glu Leu Ala Thr Gln Ile Lys Pro Pro Glu
 165 170 175
 Val Leu Glu Asn Gln Glu Lys Glu Asp Leu Leu Lys Lys Gln Glu Gly
 180 185 190
 Ala Val Asp Thr Phe Thr Leu Ile His His Glu Leu Glu Ile Ser Thr
 195 200 205
 Asn Pro Ala Gln Tyr Ala Met Ile Leu Asp Ile Val Asn Asn Leu Leu
 210 215 220
 Leu His Val Glu Pro Lys Arg Lys Glu His Ser Glu Lys Lys Gln Arg
 225 230 235 240
 Val Arg Phe Gln Leu Glu Ile Ser Ser Asn Pro Glu Glu Gln Arg Ser
 245 250 255
 Ser Ile Leu His Leu Gln Glu Ala Val Arg Gln His Val Ala Gln Ile
 260 265 270
 Arg Gln Leu Glu Lys Gln Met Tyr Ser Ile Met Lys Ser Leu Gln Asp
 275 280 285
 Asp Ser Lys Asn Glu Asn Leu Leu Asp Leu Asn Gln Lys Leu Gln Leu
 290 295 300
 Gln Leu Asn Gln Glu Lys Ala Asn Leu Gln Leu Glu Ser Glu Glu Leu
 305 310 315 320
 Asn Ile Leu Ile Arg Cys Phe Lys Asp Phe Gln Leu Gln Arg Ala Asn
 325 330 335
 Lys Met Glu Leu Arg Lys His Lys Lys Met
 340 345

<210> 578

<211> 91

<212> PRT

<213> Homo sapiens

<400> 578

Arg His Glu Gly His Leu Gly Ser Gly Arg Asn Gly Gly Gly Ser Met
 1 5 10 15
 Asn Ala Pro Pro Ala Phe Glu Ser Phe Leu Leu Phe Glu Gly Glu Lys
 20 25 30

Ile Thr Ile Asn Lys Asp Thr Lys Val Pro Asn Ala Cys Leu Phe Thr
35 40 45
Ile Asn Lys Glu Asp His Thr Leu Gly Asn Ile Ile Lys Ser Arg Ala
50 55 60
Cys Phe Pro Phe Ala Phe Cys Arg Asp Cys Gln Phe Pro Glu Ala Ser
65 70 75 80
Pro Ala Thr Leu Pro Val Gln Pro Ala Glu Leu
85 90

<210> 579
<211> 331
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (18)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (20)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (300)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (311)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (313)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (320)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE

<222> (325)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 579

Gly Arg Pro Thr Arg Pro Gly Gly Leu Gly Ser Gly Val Leu Ala Leu
 1 5 10 15
 Ala Xaa Gly Xaa Pro Ala Arg Leu Ala Gly Thr Val His Glu Val Gly
 20 25 30
 Asp Ala Pro Arg Arg Ala Pro Asp Gln Ala Ala Glu Ile Gly Ser Arg
 35 40 45
 Gly Ser Thr Lys Ala Gln Gly Pro Gln Gln Gln Pro Gly Ser Glu Gly
 50 55 60
 Pro Ser Tyr Ala Lys Lys Val Ala Leu Trp Leu Ala Gly Leu Leu Gly
 65 70 75 80
 Ala Gly Gly Thr Val Ser Val Val Tyr Ile Phe Gly Asn Asn Pro Val
 85 90 95
 Asp Glu Asn Gly Ala Lys Ile Pro Asp Glu Phe Asp Asn Asp Pro Ile
 100 105 110
 Leu Val Gln Gln Leu Arg Arg Thr Tyr Lys Tyr Phe Lys Asp Tyr Arg
 115 120 125
 Gln Met Ile Ile Glu Pro Thr Ser Pro Cys Leu Leu Pro Asp Pro Leu
 130 135 140
 Gln Glu Pro Tyr Tyr Gln Pro Pro Tyr Thr Leu Val Leu Glu Leu Thr
 145 150 155 160
 Gly Val Leu Leu His Pro Glu Trp Ser Leu Ala Thr Gly Trp Arg Phe
 165 170 175
 Lys Lys Arg Pro Gly Ile Glu Thr Leu Phe Gln Gln Leu Ala Pro Leu
 180 185 190
 Tyr Glu Ile Val Ile Phe Thr Ser Glu Thr Gly Met Thr Ala Phe Pro
 195 200 205
 Leu Ile Asp Ser Val Asp Pro His Gly Phe Ile Ser Tyr Arg Leu Phe
 210 215 220
 Arg Asp Ala Thr Arg Tyr Met Asp Gly His His Val Lys Asp Ile Ser
 225 230 235 240
 Cys Leu Asn Arg Asp Pro Ala Arg Val Val Val Val Asp Cys Lys Lys
 245 250 255

535

Glu Ala Phe Arg Leu Gln Pro Tyr Asn Gly Val Ala Leu Arg Pro Trp
260 265 270

Asp Gly Asn Ser Asp Asp Arg Val Leu Leu Asp Leu Ser Ala Phe Leu
275 280 285

Lys Thr Ile Ala Leu Asn Gly Val Gly Gly Arg Xaa Glu Pro Cys Trp
290 295 300

Glu His Tyr Ala Leu Gly Xaa Asp Xaa Pro Arg Trp Ala Ala Phe Xaa
305 310 315 320

Asn Ser Gly Lys Xaa Gly Leu Glu Ala Gly Arg
325 330

<210> 580

<211> 374

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (235)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (285)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (307)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (319)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (324)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (341)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (359)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 580

Pro Ser Thr Val Arg Asn Ser Arg Val Asp Pro Arg Val Arg Pro Arg
1 5 10 15

Val Arg Ala Gly Val Ala Ala Leu Ala Thr Val Gly Val Ala Ser Gly
20 25 30

Pro Gly Pro Gly Arg Pro Gly Pro Leu Gln Asp Glu Thr Leu Gly Val
35 40 45

Ala Ser Val Pro Ser Gln Trp Arg Ala Val Gln Gly Ile Arg Gly Glu
50 55 60

Thr Lys Ser Cys Gln Thr Ala Ser Ile Ala Thr Ala Ser Ala Ser Ala
65 70 75 80

Gln Ala Arg Asn His Val Asp Ala Gln Val Gln Thr Glu Ala Pro Val
85 90 95

Pro Val Ser Val Gln Pro Pro Ser Gln Tyr Asp Ile Pro Arg Leu Ala
100 105 110

Ala Phe Leu Arg Arg Val Glu Ala Met Val Ile Arg Glu Leu Asn Lys
115 120 125

Asn Trp Gln Ser His Ala Phe Asp Gly Phe Glu Val Asn Trp Thr Glu
130 135 140

Gln Gln Gln Met Val Ser Cys Leu Tyr Thr Leu Gly Tyr Pro Pro Ala
145 150 155 160

Gln Ala Gln Gly Leu His Val Thr Ser Ile Ser Trp Asn Ser Thr Gly
165 170 175

Ser Val Val Ala Cys Ala Tyr Gly Arg Leu Asp His Gly Asp Trp Ser
180 185 190

Thr Leu Lys Ser Phe Val Cys Ala Trp Asn Leu Asp Arg Arg Asp Leu
195 200 205

Arg Pro Gln Gln Pro Ser Ala Val Val Glu Val Pro Ser Ala Val Leu
210 215 220

Cys Leu Ala Phe His Pro Thr Gln Pro Ser Xaa Val Ala Gly Gly Leu

537

225 230 235 240
 Tyr Ser Gly Glu Val Leu Val Trp Asp Leu Ser Arg Leu Glu Asp Pro
 245 250 255
 Leu Leu Trp Arg Thr Gly Leu Thr Asp Asp Thr His Thr Asp Pro Val
 260 265 270
 Ser Gln Val Val Trp Leu Pro Glu Pro Gly His Ser Xaa Arg Phe Gln
 275 280 285
 Val Leu Ser Val Ala Thr Asp Gly Lys Val Leu Leu Trp Gln Gly Ile
 290 295 300
 Gly Val Xaa Gln Leu Gln Phe Thr Glu Gly Phe Ala Trp Phe Xaa Gln
 305 310 315 320
 Gln Leu Pro Xaa Ser Thr Lys Leu Lys Lys His Pro Arg Gly Arg Pro
 325 330 335
 Arg Trp Ala Pro Xaa Gln Ala Phe Phe Gln Phe Asp Leu Arg Phe Ser
 340 345 350
 Phe Trp Gln Glu Ala Val Xaa Val Gln Phe Ser Trp His Trp Arg Ala
 355 360 365
 Ala Leu Arg Gly Ala His
 370

<210> 581

<211> 94

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (80)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (90)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 581

Cys Pro Asp Gln Asn Gly Trp Ala Ser Phe Gly Ala Pro Leu Ser Ala
 1 5 10 15

Gly Gly Gln Pro Cys Tyr Leu Leu Asp Ile Gly Cys Gly Ser Gly Leu

20 25 30
 Ser Gly Asp Tyr Leu Ser Asp Glu Gly His Tyr Trp Val Gly Ile Asp
 35 40 45
 Ile Ser Pro Ala Met Leu Asp Ala Ala Leu Asp Arg Asp Thr Glu Gly
 50 55 60
 Asp Leu Leu Leu Gly Asp Met Gly Gln Gly Ile Pro Phe Lys Pro Xaa
 65 70 75 80
 Ser Leu Met Asp Val Ser Ala Phe Cys Xaa Ser Val Ala Leu
 85 90

 <210> 582
 <211> 163
 <212> PRT
 <213> Homo sapiens

 <400> 582
 Pro Thr Arg Pro Ala Ala Gly Gly Ala Glu Arg Ile Ala Gly Ser Ala
 1 5 10 15
 Met Ser Ser Glu Pro Pro Pro Pro Pro Gln Pro Pro Thr His Gln Ala
 20 25 30
 Ser Val Gly Leu Leu Asp Thr Pro Arg Ser Arg Glu Arg Ser Pro Ser
 35 40 45
 Pro Leu Arg Gly Asn Val Val Pro Ser Pro Leu Pro Thr Arg Arg Thr
 50 55 60
 Arg Thr Phe Ser Ala Thr Val Arg Ala Ser Gln Gly Pro Val Tyr Lys
 65 70 75 80
 Gly Val Cys Lys Cys Phe Cys Arg Ser Lys Gly His Gly Phe Ile Thr
 85 90 95
 Pro Ala Asp Gly Gly Pro Asp Ile Phe Leu His Ile Ser Asp Val Glu
 100 105 110
 Gly Glu Tyr Val Pro Val Glu Gly Asp Glu Val Thr Tyr Lys Met Cys
 115 120 125
 Ser Ile Pro Pro Lys Asn Glu Lys Leu Gln Ala Val Glu Val Val Ile
 130 135 140
 Thr His Leu Ala Pro Gly Thr Lys His Glu Thr Trp Ser Gly His Val
 145 150 155 160

Ile Ser Ser

<210> 583
<211> 293
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (52)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (53)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (58)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (150)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (171)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (207)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (254)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 583
Leu Leu Gly Pro Asn Leu Thr Met Gly Ser Gln Pro Gly Arg Ile Pro
1 5 10 15

Asp Leu Leu Glu Lys Gly Glu Arg Leu Pro Gln Pro Pro Ile Cys Thr

540

20 25 30
 Ile Asp Val Tyr Met Ile Met Val Lys Cys Trp Met Ile Asp Ser Glu
 35 40 45
 Cys Arg Pro Xaa Xaa Arg Glu Leu Val Xaa Glu Phe Ser Arg Met Ala
 50 55 60
 Arg Asp Pro Gln Arg Phe Val Val Ile Gln Asn Glu Asp Leu Gly Pro
 65 70 75 80
 Ala Ser Pro Leu Asp Ser Thr Phe Tyr Arg Ser Leu Leu Glu Asp Asp
 85 90 95
 Asp Met Gly Asp Leu Val Asp Ala Glu Glu Tyr Leu Val Pro Gln Gln
 100 105 110
 Gly Phe Phe Cys Pro Asp Pro Ala Pro Gly Ala Gly Gly Met Val His
 115 120 125
 His Arg His Arg Ser Ser Ser Thr Arg Ser Gly Gly Gly Asp Leu Thr
 130 135 140
 Leu Gly Leu Glu Pro Xaa Glu Arg Gly Gly Pro Gln Val Ser Thr Gly
 145 150 155 160
 Thr Leu Arg Arg Ala Gly Ser Asp Val Phe Xaa Gly Asp Leu Gly Met
 165 170 175
 Gly Ala Ala Lys Gly Leu Gln Ser Leu Pro Thr His Asp Pro Ser Pro
 180 185 190
 Leu Gln Arg Tyr Ser Glu Asp Pro Thr Val Pro Leu Pro Ser Xaa Thr
 195 200 205
 Asp Gly Tyr Val Ala Pro Leu Thr Cys Ser Pro Gln Pro Glu Tyr Val
 210 215 220
 Asn Gln Pro Asp Val Arg Pro Gln Pro Pro Ser Pro Arg Glu Gly Pro
 225 230 235 240
 Leu Pro Ala Ala Arg Pro Ala Gly Ala Thr Leu Glu Arg Xaa Lys Thr
 245 250 255
 Leu Ser Pro Gly Lys Asn Gly Val Val Lys Glu Phe Leu Pro Leu Gly
 260 265 270
 Val Pro Trp Arg Thr Pro Ser Ile Asp Thr Pro Gly Glu Gly Ala Cys
 275 280 285
 Pro Ser Ala Pro Pro

290

<210> 584

<211> 132

<212> PRT

<213> Homo sapiens

<400> 584

Gly Gly Ala Gln Pro Gly Met Glu Gly Ala Ala Ala Thr Val His Leu
1 5 10 15

Ile Ser Gln Trp Ala Val Glu Pro Asn Ala Arg Val Gly Pro Leu Leu
20 25 30

Glu Val Glu Ala Ala Ala Ala Asp His His Glu Ala Ala Ala Gly Ala
35 40 45

Gly Ser Ala Val Glu Lys Ile Cys Ile Asp Lys Gly Leu Thr Asp Glu
50 55 60

Ser Glu Ile Leu Arg Phe Leu Gln His Gly Thr Leu Val Gly Leu Leu
65 70 75 80

Pro Val Pro His Pro Ile Leu Ile Arg Lys Tyr Gln Ala Asn Ser Gly
85 90 95

Thr Ala Met Trp Phe Arg Thr Tyr Met Trp Gly Val Ile Tyr Leu Arg
100 105 110

Asn Val Asp Pro Pro Val Trp Tyr Asp Thr Asp Val Lys Leu Phe Glu
115 120 125

Ile Gln Arg Val
130

<210> 585

<211> 218

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (92)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (117)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (140)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (141)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (188)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (199)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (200)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 585

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Glu | Arg | Cys | Arg | Arg | Glu | Ala | Leu | Arg | Gly | Ser | Arg | Leu | Cys | Pro |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ala | Thr | Pro | Pro | Ser | Ala | Leu | Gly | Ser | Gln | Asp | Gly | Ser | Arg | Thr | Arg |
| | | | 20 | | | | 25 | | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Asp | Arg | Leu | Gly | Ala | Ala | Gly | Trp | Pro | Gly | Leu | Val | Val | Gly | Leu | Cys |
| | 35 | | | | | 40 | | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Pro | Ala | Ala | Gly | Xaa | Gln | Arg | Asp | Leu | Leu | His | Arg | Arg | Gly | Gly |
| | 50 | | | | 55 | | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ala | Ser | Phe | Gly | Lys | Ser | Phe | Ala | Gln | Lys | Ser | Gly | Tyr | Phe | Leu |
| 65 | | | | | 70 | | | | | 75 | | | | | 80 |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Cys | Leu | Ser | Ser | Leu | Gly | Ser | Leu | Glu | Asn | Pro | Xaa | Glu | Asn | Val | Val |
| | | | | 85 | | | | | 90 | | | | | | 95 |

Ala Asp Ile Gln Ile Val Val Asp Lys Ser Pro Leu Pro Leu Gly Phe
 100 105 110

Ser Pro Val Cys Xaa Pro Met Asp Ser Lys Ala Ser Val Ser Lys Lys
 115 120 125

Lys Arg Met Cys Val Lys Leu Leu Pro Leu Gly Xaa Xaa Asp Thr Ala
 130 135 140

Val Phe Asp Val Arg Leu Ser Gly Lys Thr Lys Thr Val Pro Gly Tyr
 145 150 155 160

Leu Arg Ile Gly Asp Met Gly Gly Phe Ala Ile Trp Cys Lys Lys Gly
 165 170 175

Gln Gly Pro Glu Ala Ser Cys Pro Lys Pro Arg Xaa Pro Gln Pro Gly
 180 185 190

Thr Cys Lys Gly Phe Ser Xaa Xaa Ala Ala Ser Gln Pro Lys Leu Arg
 195 200 205

Ala Gly Leu Leu Gly Ser Arg Thr Ser Val
 210 215

<210> 586

<211> 233

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 586

Ala Arg Gly Glu Met Glu Gly Arg Gln Val Leu Glu Val Lys Met Gln
 1 5 10 15

Val Glu Tyr Met Ser Phe Ser Ala His Ala Asp Ala Lys Gly Ile Met
 20 25 30

Gln Leu Val Gly Gln Ala Glu Pro Xaa Ser Val Leu Leu Val His Gly
 35 40 45

Glu Ala Lys Lys Met Glu Phe Leu Lys Gln Lys Ile Glu Gln Glu Leu
 50 55 60

Arg Val Asn Cys Tyr Met Pro Ala Asn Gly Glu Thr Val Thr Leu Pro

65 70 75 80
 Thr Ser Pro Ser Ile Pro Val Gly Ile Ser Leu Gly Leu Leu Lys Arg
 85 90 95
 Glu Met Ala Gln Gly Leu Leu Pro Glu Ala Lys Lys Pro Arg Leu Leu
 100 105 110
 His Gly Thr Leu Ile Met Lys Asp Ser Asn Phe Arg Leu Val Ser Ser
 115 120 125
 Glu Gln Ala Leu Lys Glu Leu Gly Leu Ala Glu His Gln Leu Arg Phe
 130 135 140
 Thr Cys Arg Val His Leu His Asp Thr Arg Lys Glu Gln Glu Thr Ala
 145 150 155 160
 Leu Arg Val Tyr Ser His Leu Lys Ser Val Leu Lys Asp His Cys Val
 165 170 175
 Gln His Leu Pro Asp Gly Ser Val Thr Val Glu Ser Val Leu Leu Gln
 180 185 190
 Ala Ala Ala Pro Ser Glu Asp Pro Gly Thr Lys Val Leu Leu Val Ser
 195 200 205
 Trp Thr Tyr Gln Asp Glu Glu Leu Gly Ser Phe Leu Thr Ser Leu Leu
 210 215 220
 Lys Lys Gly Leu Pro Gln Ala Pro Ser
 225 230

<210> 587

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (100)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 587

Gly Pro Leu Ser His His Ile Arg Ala Gln Leu Ser Lys Met Leu Leu
 1 5 10 15
 Ala Arg Lys Gln Ile Leu Cys Val Asn Val Lys Asn Phe Ala Val Ile
 20 25 30

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<400> 588
Ala Arg Ala Ala Val Gly Arg Thr Ala Gly Val Arg Thr Trp Ala Pro
  1                      5                      10                      15
Leu Ala Met Ala Ala Lys Val Asp Leu Ser Thr Ser Thr Asp Trp Lys
                20                      25                      30
Glu Ala Lys Ser Phe Leu Lys Gly Leu Ser Asp Lys Gln Arg Glu Glu
    35                      40                      45
His Tyr Phe Cys Lys Asp Phe Val Arg Leu Lys Lys Ile Pro Thr Trp
    50                      55                      60
Lys Glu Met Ala Lys Gly Val Ala Val Lys Val Glu Glu Pro Arg Tyr
  65                      70                      75                      80
Lys Lys Asp Lys Gln Leu Asn Glu Lys Ile Ser Leu Leu Arg Ser Asp
                85                      90                      95
Ile Thr Lys Leu Glu Val Asp Ala Ile Val Asn Ala Ala Asn Ser Ser
    100                      105                      110
Pro Pro Pro Arg Ser Leu Ile Lys Asp Leu Arg Cys Gly Lys Lys Lys
    115                      120                      125
Lys Lys Lys Lys Lys

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130

<210> 589

<211> 163

<212> PRT

<213> Homo sapiens

<400> 589

Arg His Arg Gly Gln Pro Leu Arg Gln Thr Arg Ala Ser Ser Ser Pro
1 5 10 15
Gln Leu Ala Gly Arg Ser Ser Ser Val Leu Pro Ala Ala Ala Gln Pro
20 25 30
Cys Thr Pro Thr Met Asp Val Phe Lys Lys Gly Phe Ser Ile Ala Lys
35 40 45
Glu Gly Val Val Gly Ala Val Glu Lys Thr Lys Gln Gly Val Thr Glu
50 55 60
Ala Ala Glu Lys Thr Lys Glu Gly Val Met Tyr Val Gly Ala Lys Thr
65 70 75 80
Lys Glu Asn Val Val Gln Ser Val Thr Ser Val Ala Glu Lys Thr Lys
85 90 95
Glu Gln Ala Asn Ala Val Ser Glu Ala Val Val Ser Ser Val Asn Thr
100 105 110
Val Ala Thr Lys Thr Val Glu Glu Ala Glu Asn Ile Ala Val Thr Ser
115 120 125
Gly Val Val Arg Lys Glu Asp Leu Arg Pro Ser Ala Pro Gln Gln Glu
130 135 140
Gly Glu Ala Ser Lys Glu Lys Glu Glu Val Ala Glu Glu Ala Gln Ser
145 150 155 160
Gly Gly Asp

<210> 590

<211> 59

<212> PRT

<213> Homo sapiens

<400> 590

547

Arg Ala Leu Leu Cys Leu Gly His His Pro Leu Leu Ala Gln Gly Val
 1 5 10 15

Pro Ala Leu Ser Asp Met Arg Leu Pro Thr Leu Leu Pro Ser Ser Pro
 20 25 30

Trp Pro Pro Leu Ala Cys Pro Pro Val Leu Leu His Gln Pro His Cys
 35 40 45

Pro Pro Ser Ala Pro Pro Thr Leu Trp Ser Phe
 50 55

<210> 591

<211> 116

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 591

Val His Ala Glu Ala Gly Arg Leu Cys His Gly Asp Cys Pro Arg Leu
 1 5 10 15

Cys Arg Pro Arg Gln Arg Ser Ala Pro Val Gln Val Tyr Thr Xaa Arg
 20 25 30

Gln Ala Ala Leu His Gly Arg Pro Gln Arg Asp Pro Cys Val Gly Gly
 35 40 45

Pro Arg Pro Leu Arg Cys Ser Arg Asp Cys Gly Gly Gly His Gln Arg
 50 55 60

Leu Val Met Pro Gly Thr Trp Thr Gln Ala Trp Gln Arg Arg Gln Val
 65 70 75 80

Val Asn Gly Leu Met Leu Gly Gln Ala Arg Ile His Val Asn Arg Leu
 85 90 95

Glu Gln Ala Val Val Asn Leu Ala Pro Cys Glu Tyr Phe His Thr Cys
 100 105 110

Cys Pro Phe Ala
 115

<210> 592
 <211> 290
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (30)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (239)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 592
 Arg Arg Ser Leu Asn Thr His Gly Ser Gly Val Ser Val Cys Leu Gln
 1 5 10 15
 Ser Leu Thr Leu Leu Ala Thr Leu Cys Pro Gly Asp Gln Xaa Ser Leu
 20 25 30
 Gly Leu Leu Thr Pro Cys Tyr Ser Gly Ser Glu Pro Ser Gly Thr Phe
 35 40 45
 Gly Pro Val Asn Pro Ser Leu Asn Asn Thr Tyr Glu Phe Met Ser Thr
 50 55 60
 Phe Phe Leu Glu Val Ser Ser Val Phe Pro Asp Phe Tyr Leu His Leu
 65 70 75 80
 Gly Gly Asp Glu Val Asp Phe Thr Cys Trp Lys Ser Asn Pro Glu Ile
 85 90 95
 Gln Asp Phe Met Arg Lys Lys Gly Phe Gly Glu Asp Phe Lys Gln Leu
 100 105 110
 Glu Ser Phe Tyr Ile Gln Thr Leu Leu Asp Ile Val Ser Ser Tyr Gly
 115 120 125
 Lys Gly Tyr Val Val Trp Gln Glu Val Phe Asp Asn Lys Val Lys Ile
 130 135 140
 Gln Pro Asp Thr Ile Ile Gln Val Trp Arg Glu Asp Ile Pro Val Asn
 145 150 155 160
 Tyr Met Lys Glu Leu Glu Leu Val Thr Lys Ala Gly Phe Arg Ala Leu
 165 170 175
 Leu Ser Ala Pro Trp Tyr Leu Asn Arg Ile Ser Tyr Gly Pro Asp Trp
 180 185 190

Lys Asp Phe Tyr Val Val Glu Pro Leu Ala Phe Glu Gly Thr Pro Glu
 195 200 205
 Gln Lys Ala Leu Val Ile Gly Gly Glu Ala Cys Met Trp Gly Glu Tyr
 210 215 220
 Val Asp Asn Thr Asn Leu Val Pro Arg Leu Trp Pro Arg Ala Xaa Ala
 225 230 235 240
 Val Ala Glu Arg Leu Trp Ser Asn Lys Leu Thr Ser Asp Leu Thr Phe
 245 250 255
 Ala Tyr Glu Arg Leu Ser His Phe Arg Cys Glu Leu Leu Arg Arg Gly
 260 265 270
 Val Gln Ala Gln Pro Leu Asn Val Gly Phe Cys Glu Gln Glu Phe Glu
 275 280 285
 Gln Thr
 290

<210> 593

<211> 665

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 593

Asp Ala Asp Gly Arg Met Asp Xaa Leu Val Ser Glu Cys Ser Ala Arg
 1 5 10 15
 Leu Leu Gln Gln Glu Glu Ile Lys Ser Leu Thr Ala Glu Ile Asp
 20 25 30
 Arg Leu Lys Asn Cys Gly Cys Leu Gly Ala Ser Pro Asn Leu Glu Gln
 35 40 45
 Leu Gln Glu Glu Asn Leu Lys Leu Lys Tyr Arg Leu Asn Ile Leu Arg
 50 55 60
 Lys Ser Leu Gln Ala Glu Arg Asn Lys Pro Thr Lys Asn Met Ile Asn
 65 70 75 80
 Ile Ile Ser Arg Leu Gln Glu Val Phe Gly His Ala Ile Lys Ala Ala

550

| | 85 | 90 | 95 |
|---|-----|-----|-----|
| Tyr Pro Asp Leu Glu Asn Pro Pro Leu Leu Val Thr Pro Ser Gln Gln | 100 | 105 | 110 |
| Ala Lys Phe Gly Asp Tyr Gln Cys Asn Ser Ala Met Gly Ile Ser Gln | 115 | 120 | 125 |
| Met Leu Lys Thr Lys Glu Gln Lys Val Asn Pro Arg Glu Ile Ala Glu | 130 | 135 | 140 |
| Asn Ile Thr Lys His Leu Pro Asp Asn Glu Cys Ile Glu Lys Val Glu | 145 | 150 | 155 |
| Ile Ala Gly Pro Gly Phe Ile Asn Val His Leu Arg Lys Asp Phe Val | 165 | 170 | 175 |
| Ser Glu Gln Leu Thr Ser Leu Leu Val Asn Gly Val Gln Leu Pro Ala | 180 | 185 | 190 |
| Leu Gly Glu Asn Lys Lys Val Ile Val Asp Phe Ser Ser Pro Asn Ile | 195 | 200 | 205 |
| Ala Lys Glu Met His Val Gly His Leu Arg Ser Thr Ile Ile Gly Glu | 210 | 215 | 220 |
| Ser Ile Ser Arg Leu Phe Glu Phe Ala Gly Tyr Asp Val Leu Arg Leu | 225 | 230 | 235 |
| Asn His Val Gly Asp Trp Gly Thr Gln Phe Gly Met Leu Ile Ala His | 245 | 250 | 255 |
| Leu Gln Asp Lys Phe Pro Asp Tyr Leu Thr Val Ser Pro Pro Ile Gly | 260 | 265 | 270 |
| Asp Leu Gln Val Phe Tyr Lys Glu Ser Lys Lys Arg Phe Asp Thr Glu | 275 | 280 | 285 |
| Glu Glu Phe Lys Lys Arg Ala Tyr Gln Cys Val Val Leu Leu Gln Gly | 290 | 295 | 300 |
| Lys Asn Pro Asp Ile Thr Lys Ala Trp Lys Leu Ile Cys Asp Val Ser | 305 | 310 | 315 |
| Arg Gln Glu Leu Asn Lys Ile Tyr Asp Ala Leu Asp Val Ser Leu Ile | 325 | 330 | 335 |
| Glu Arg Gly Glu Ser Phe Tyr Gln Asp Arg Met Asn Asp Ile Val Lys | 340 | 345 | 350 |
| Glu Phe Glu Asp Arg Gly Phe Val Gln Val Asp Asp Gly Arg Lys Ile | | | |

| | | |
|---|-----|-------------|
| 355 | 360 | 365 |
| Val Phe Val Pro Gly Cys Ser Ile Pro Leu Thr Ile Val Lys Ser Asp | | |
| 370 | 375 | 380 |
| Gly Gly Tyr Thr Tyr Asp Thr Ser Asp Leu Ala Ala Ile Lys Gln Arg | | |
| 385 | 390 | 400 |
| Leu Phe Glu Glu Lys Ala Asp Met Ile Ile Tyr Val Val Asp Asn Gly | | |
| | 405 | 410 415 |
| Gln Ser Val His Phe Gln Thr Ile Phe Ala Ala Ala Gln Met Ile Gly | | |
| | 420 | 425 430 |
| Trp Tyr Asp Pro Lys Val Thr Arg Val Phe His Ala Gly Phe Gly Val | | |
| | 435 | 440 445 |
| Val Leu Gly Glu Asp Lys Lys Lys Phe Lys Thr Arg Ser Gly Glu Thr | | |
| | 450 | 455 460 |
| Val Arg Leu Met Asp Leu Leu Gly Glu Gly Leu Lys Arg Ser Met Asp | | |
| | 465 | 470 475 480 |
| Lys Leu Lys Glu Lys Glu Arg Asp Lys Val Leu Thr Ala Glu Glu Leu | | |
| | 485 | 490 495 |
| Asn Ala Ala Gln Thr Ser Val Ala Tyr Gly Cys Ile Lys Tyr Ala Asp | | |
| | 500 | 505 510 |
| Leu Ser His Asn Arg Leu Asn Asp Tyr Ile Phe Ser Phe Asp Lys Met | | |
| | 515 | 520 525 |
| Leu Asp Asp Arg Gly Asn Thr Ala Ala Tyr Leu Leu Tyr Ala Phe Thr | | |
| | 530 | 535 540 |
| Arg Ile Arg Ser Ile Ala Arg Leu Ala Asn Ile Asp Glu Glu Met Leu | | |
| | 545 | 550 555 560 |
| Gln Lys Ala Ala Arg Glu Thr Lys Ile Leu Leu Asp His Glu Lys Glu | | |
| | 565 | 570 575 |
| Trp Lys Leu Gly Arg Cys Ile Leu Arg Phe Pro Glu Ile Leu Gln Lys | | |
| | 580 | 585 590 |
| Ile Leu Asp Asp Leu Phe Leu His Thr Leu Cys Asp Tyr Ile Tyr Glu | | |
| | 595 | 600 605 |
| Leu Ala Thr Ala Phe Thr Glu Phe Tyr Asp Ser Cys Tyr Cys Val Glu | | |
| | 610 | 615 620 |
| Lys Asp Arg Gln Thr Gly Lys Ile Leu Lys Val Asn Met Trp Arg Met | | |

625 630 635 640
 Leu Leu Cys Glu Ala Val Ala Ala Val Met Ala Lys Gly Phe Asp Ile
 645 650 655

Leu Gly Ile Lys Pro Val Gln Arg Met
 660 665

<210> 594
 <211> 116
 <212> PRT
 <213> Homo sapiens

<400> 594
 Thr Val Thr Glu Thr Thr Val Thr Val Thr Thr Glu Pro Glu Asn Arg
 1 5 10 15
 Ser Leu Thr Ile Lys Leu Arg Lys Arg Lys Pro Glu Lys Lys Val Glu
 20 25 30
 Trp Thr Ser Asp Thr Val Asp Asn Glu His Met Gly Arg Arg Ser Ser
 35 40 45
 Lys Cys Cys Cys Ile Tyr Glu Lys Pro Arg Ala Phe Gly Glu Ser Ser
 50 55 60
 Thr Glu Ser Asp Glu Glu Glu Glu Gly Cys Gly His Thr His Cys
 65 70 75 80
 Val Arg Gly His Arg Lys Gly Arg Arg Arg Ala Thr Leu Gly Pro Thr
 85 90 95
 Pro Thr Thr Pro Pro Gln Pro Pro Asp Pro Ser Gln Pro Pro Pro Gly
 100 105 110
 Pro Met Gln His
 115

<210> 595
 <211> 294
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (269)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (278)

<223> xaa equals any of the naturally occurring L-amino acids

<400> 595

Thr Gln Leu Arg Val Ser Glu Arg Glu Gly Pro Gly Asp Pro Gln Arg
 1 5 10 15
 Phe Ser Asp His Thr Leu Arg Thr Pro Arg Leu Glu Asp Arg Pro Gly
 20 25 30
 Asp Ala Met Trp Gly Glu Gly Leu Arg Ala Trp Cys Arg Phe Val Glu
 35 40 45
 Asn Arg Trp Cys Leu Lys Arg Val Ser Ala Pro Leu His Leu Gly Leu
 50 55 60
 Leu Gly Cys Pro Asp Ala Glu Ala His Phe Pro Ala Met Leu Thr Leu
 65 70 75 80
 Pro Leu Ser Pro Pro Ser Arg Lys Met Ala Thr Asn Phe Leu Ala His
 85 90 95
 Glu Lys Ile Trp Phe Asp Lys Phe Lys Tyr Asp Asp Ala Glu Arg Arg
 100 105 110
 Phe Tyr Glu Gln Met Asn Gly Pro Val Ala Gly Ala Ser Arg Gln Glu
 115 120 125
 Asn Gly Ala Ser Val Ile Leu Arg Asp Ile Ala Arg Ala Arg Glu Asn
 130 135 140
 Ile Gln Lys Ser Leu Ala Gly Ser Ser Gly Pro Gly Ala Ser Ser Gly
 145 150 155 160
 Thr Ser Gly Asp His Gly Glu Leu Val Val Arg Ile Ala Ser Leu Glu
 165 170 175
 Val Glu Asn Gln Ser Leu Arg Gly Val Val Gln Glu Leu Gln Gln Ala
 180 185 190
 Ile Ser Lys Leu Glu Ala Arg Leu Asn Val Leu Glu Lys Ser Ser Pro
 195 200 205
 Gly His Arg Ala Thr Ala Pro Gln Thr Gln His Val Ser Pro Met Arg
 210 215 220
 Gln Val Glu Pro Pro Ala Lys Lys Pro Ala Thr Pro Ala Glu Asp Asp
 225 230 235 240

Glu Asp Asp Asp Ile Asp Leu Phe Gly Ser Asp Asn Glu Glu Glu Asp
245 250 255
Lys Glu Ala Ala Gln Leu Arg Glu Glu Arg Leu Arg Xaa Tyr Ala Glu
260 265 270
Lys Lys Ala Lys Lys Xaa Ala Leu Val Ala Lys Ser Ser Ile Leu Leu
275 280 285
Asp Phe Lys Pro Trp Gly
290

<210> 596
<211> 134
<212> PRT
<213> Homo sapiens

<400> 596
Val Ser Arg Leu Gly Leu Leu Thr Pro Leu Gly Cys Ser Phe Gly Thr
1 5 10 15
Asp Glu Trp Leu Cys Pro Val Thr Ala Leu Ser Leu Pro Gly Gly Tyr
20 25 30
Val His Ser Arg Pro Leu Pro Arg Leu Arg Pro Met Arg Tyr Gly Asp
35 40 45
Thr Leu Ala Pro Arg Ser Trp Arg His Arg Pro Leu Pro Trp His Ser
50 55 60
Ser Phe Ala Gly Asp Pro Pro Leu Pro Lys Ala Leu Ser Pro Cys Ser
65 70 75 80
His Ser Arg Arg Thr Ala Ala Arg Ala Ser Gly Ser Leu Ala Thr Gly
85 90 95
Phe Glu Arg Leu His Ser Trp Gly Leu Glu Gly Gly Val Pro Lys Ala
100 105 110
Leu Ser Lys Ser Gln Ser Ser Ser His Gln Ser Leu Tyr Lys Val Leu
115 120 125
Gly Pro Glu Ala Leu Pro
130

<210> 597

<211> 91

<212> PRT

<213> Homo sapiens

<400> 597

Glu Gly Pro Glu Gly Ala Asn Leu Phe Ile Tyr His Leu Pro Gln Glu
1 5 10 15
Phe Gly Asp Gln Asp Ile Leu Gln Met Phe Met Pro Phe Gly Asn Val
20 25 30
Ile Ser Ala Lys Val Phe Ile Asp Lys Gln Thr Asn Leu Ser Lys Cys
35 40 45
Phe Gly Phe Val Ser Tyr Asp Asn Pro Val Ser Ala Gln Ala Ala Ile
50 55 60
Gln Ala Met Asn Gly Phe Gln Ile Gly Met Lys Arg Leu Lys Val Gln
65 70 75 80
Leu Lys Arg Ser Lys Asn Asp Ser Lys Pro Tyr
85 90

<210> 598

<211> 68

<212> PRT

<213> Homo sapiens

<400> 598

Arg Pro Thr Arg Pro Glu Lys Val Gly Ser Gly Gly Ser Ser Val Gly
1 5 10 15
Ser Gly Asp Ala Ser Ser Ser Arg His His His Arg Arg Arg Arg Phe
20 25 30
His Leu Pro Gln Gln Pro Leu Leu Gln Arg Glu Val Trp Cys Val Gly
35 40 45
Thr Thr Gly Asn Ala Asn Gln Ala Gln Ser Ser Thr Glu Gln Thr Leu
50 55 60
Leu Lys Pro Lys
65

<210> 599

<211> 119

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (58)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (68)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (88)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (98)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (99)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 599

Phe Gly Arg Asp Gln Val Tyr Leu Ser Tyr Asn Asn Val Ser Ser Leu
1 5 10 15

Lys Met Leu Val Ala Lys Asp Asn Trp Val Leu Ser Ser Glu Ile Ser
20 25 30

Gln Val Arg Leu Tyr Thr Leu Glu Asp Asp Lys Phe Leu Ser Phe His
35 40 45

Met Glu Met Val Val His Val Asp Ala Xaa Gln Ala Phe Leu Leu Leu
50 55 60

Ser Asp Leu Xaa Gln Arg Pro Glu Trp Asp Lys His Tyr Arg Ser Val
65 70 75 80

Glu Leu Val Gln Gln Val Asp Xaa Gly Arg Arg His Leu Pro Arg His
85 90 95

Gln Xaa Xaa Pro Arg Arg Ser His Lys Ala Pro Gly Leu Arg Asp Pro
100 105 110

Gly Leu Glu Ala Glu Ala Leu
115

<210> 600
 <211> 177
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (1)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (8)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (69)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (135)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 600
 Xaa Glu Arg Leu Arg Ala Gln Xaa Glu Lys Ser Arg Asp Ser Gln Pro
 1 5 10 15
 Arg Leu Pro Leu Arg Phe Pro Ser Trp Arg Gly Pro Trp Cys Gly Ile
 20 25 30
 Glu Ile Ala Gly Tyr Gly Ala Glu Val Phe Arg Gln Tyr Trp Asp Ile
 35 40 45
 Pro Asp Gly Thr Asp Cys His Arg Lys Ala Tyr Ser Thr Thr Ser Ile
 50 55 60
 Ala Ser Val Ala Xaa Leu Thr Ala Ala Ala Tyr Arg Val Thr Leu Asn
 65 70 75 80
 Pro Pro Gly Thr Phe Leu Glu Gly Val Ala Lys Val Gly Gln Tyr Thr
 85 90 95
 Phe Thr Ala Ala Ala Val Gly Ala Val Phe Gly Leu Thr Thr Cys Ile
 100 105 110
 Ser Ala His Val Arg Glu Lys Pro Asp Asp Pro Leu Asn Tyr Phe Leu

115 120 125
 Gly Gly Cys Ala Gly Gly Xaa Thr Leu Gly Ala Arg Thr His Asn Tyr
 130 135 140
 Gly Ile Gly Ala Ala Ala Cys Val Tyr Phe Gly Ile Ala Ala Ser Leu
 145 150 155 160
 Val Lys Met Gly Arg Leu Glu Gly Trp Glu Val Phe Ala Lys Pro Lys
 165 170 175
 Val

 <210> 601
 <211> 218
 <212> PRT
 <213> Homo sapiens

 <400> 601
 Arg Gly Gly Gly Gly Gly Ala Ser Ser Cys Cys Cys Cys Ala Pro Ser
 1 5 10 15
 Pro Arg Gly Arg Pro Val Pro Ala Arg Thr Pro Arg Arg Cys Pro Arg
 20 25 30
 Pro Ser Pro Gly Pro Ala Met Gly Leu Thr Val Ser Ala Leu Phe Ser
 35 40 45
 Arg Ile Phe Gly Lys Lys Gln Met Arg Ile Leu Met Val Gly Leu Asp
 50 55 60
 Ala Ala Gly Lys Thr Thr Ile Leu Tyr Lys Leu Lys Leu Gly Glu Ile
 65 70 75 80
 Val Thr Thr Ile Pro Thr Ile Gly Phe Asn Val Glu Thr Val Glu Tyr
 85 90 95
 Lys Asn Ile Cys Phe Thr Val Trp Asp Val Gly Gly Gln Asp Lys Ile
 100 105 110
 Arg Pro Leu Trp Arg His Tyr Phe Gln Asn Thr Gln Gly Leu Ile Phe
 115 120 125
 Val Val Asp Ser Asn Asp Arg Glu Arg Val Gln Glu Ser Ala Asp Glu
 130 135 140
 Leu Gln Lys Met Leu Gln Glu Asp Glu Leu Arg Asp Ala Val Leu Leu
 145 150 155 160

Val Phe Ala Asn Lys Gln Asp Met Pro Asn Ala Met Pro Val Ser Glu
 165 170 175

Leu Thr Asp Lys Leu Gly Leu Gln His Leu Arg Ser Arg Thr Trp Tyr
 180 185 190

Val Gln Ala Thr Cys Ala Thr Gln Gly Thr Gly Leu Tyr Asp Gly Leu
 195 200 205

Asp Trp Leu Ser His Glu Leu Ser Lys Arg
 210 215

<210> 602

<211> 829

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (32)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (454)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 602

Pro Gly Gln Ala Gly Ala Glu Gly His Val Arg Cys Cys Pro Gly Glu
 1 5 10 15

Glu Gln Lys Ala Gly Gly Glu Arg Arg Cys Pro Gly Pro Gln Arg Xaa
 20 25 30

Gly Ala Ala Leu Gly Pro Gly Pro Gly Glu Ala Arg Leu Asp Tyr Ser
 35 40 45

Glu Phe Phe Thr Glu Asp Val Gly Gln Leu Pro Gly Leu Thr Ile Trp
 50 55 60

Gln Ile Glu Asn Phe Val Pro Val Leu Val Glu Glu Ala Phe His Gly
 65 70 75 80

Lys Phe Tyr Glu Ala Asp Cys Tyr Ile Val Leu Lys Thr Phe Leu Asp
 85 90 95

Asp Ser Gly Ser Leu Asn Trp Glu Ile Tyr Tyr Trp Ile Gly Gly Glu
 100 105 110

Ala Thr Leu Asp Lys Lys Ala Cys Ser Ala Ile His Ala Val Asn Leu
115 120 125

Arg Asn Tyr Leu Gly Ala Glu Cys Arg Thr Val Arg Glu Glu Met Gly
130 135 140

Asp Glu Ser Glu Glu Phe Leu Gln Val Phe Asp Asn Asp Ile Ser Tyr
145 150 155 160

Ile Glu Gly Gly Thr Ala Ser Gly Phe Tyr Thr Val Glu Asp Thr His
165 170 175

Tyr Val Thr Arg Met Tyr Arg Val Tyr Gly Lys Lys Asn Ile Lys Leu
180 185 190

Glu Pro Val Pro Leu Lys Gly Thr Ser Leu Asp Pro Arg Phe Val Phe
195 200 205

Leu Leu Asp Arg Gly Leu Asp Ile Tyr Val Trp Arg Gly Ala Gln Ala
210 215 220

Thr Leu Ser Ser Thr Thr Lys Ala Arg Leu Phe Ala Glu Lys Ile Asn
225 230 235 240

Lys Asn Glu Arg Lys Gly Lys Ala Glu Ile Thr Leu Leu Val Gln Gly
245 250 255

Gln Glu Leu Pro Glu Phe Trp Glu Ala Leu Gly Gly Glu Pro Ser Glu
260 265 270

Ile Lys Lys His Val Pro Glu Asp Phe Trp Pro Pro Gln Pro Lys Leu
275 280 285

Tyr Lys Val Gly Leu Gly Leu Gly Tyr Leu Glu Leu Pro Gln Ile Asn
290 295 300

Tyr Lys Leu Ser Val Glu His Lys Gln Arg Pro Lys Val Glu Leu Met
305 310 315 320

Pro Arg Met Arg Leu Leu Gln Ser Leu Leu Asp Thr Arg Cys Val Asn
325 330 335

Ile Leu Asp Cys Trp Ser Asp Val Phe Ile Trp Leu Gly Arg Lys Ser
340 345 350

Pro Arg Leu Val Arg Ala Ala Ala Leu Lys Leu Gly Gln Glu Leu Cys
355 360 365

Gly Met Leu His Arg Pro Arg His Ala Thr Val Ser Arg Ser Leu Glu
370 375 380

Gly Thr Glu Ala Gln Val Phe Lys Ala Lys Phe Lys Asn Trp Asp Asp
 385 390 395 400
 Val Leu Thr Val Asp Tyr Thr Arg Asn Ala Glu Ala Val Leu Gln Ser
 405 410 415
 Pro Gly Leu Ser Gly Lys Val Lys Arg Asp Ala Glu Lys Lys Asp Gln
 420 425 430
 Met Lys Ala Asp Leu Thr Ala Leu Phe Leu Pro Arg Gln Pro Pro Met
 435 440 445
 Ser Leu Ala Glu Ala Xaa Gln Leu Met Glu Glu Trp Asn Glu Asp Leu
 450 455 460
 Asp Gly Met Glu Gly Phe Val Leu Glu Gly Lys Lys Phe Ala Arg Leu
 465 470 475 480
 Pro Glu Glu Glu Phe Gly His Phe Tyr Thr Gln Asp Cys Tyr Val Phe
 485 490 495
 Leu Cys Arg Tyr Trp Val Pro Val Glu Tyr Glu Glu Glu Lys Lys
 500 505 510
 Glu Asp Lys Glu Glu Lys Ala Glu Gly Lys Glu Gly Glu Glu Ala Thr
 515 520 525
 Ala Glu Ala Glu Glu Lys Gln Pro Glu Glu Asp Phe Gln Cys Ile Val
 530 535 540
 Tyr Phe Trp Gln Gly Arg Glu Ala Ser Asn Met Gly Trp Leu Thr Phe
 545 550 555 560
 Thr Phe Ser Leu Gln Lys Lys Phe Glu Ser Leu Phe Pro Gly Lys Leu
 565 570 575
 Glu Val Val Arg Met Thr Gln Gln Gln Glu Asn Pro Lys Phe Leu Ser
 580 585 590
 His Phe Lys Arg Lys Phe Ile Ile His Arg Gly Lys Arg Lys Ala Val
 595 600 605
 Gln Gly Ala Gln Gln Pro Ser Leu Tyr Gln Ile Arg Thr Asn Gly Ser
 610 615 620
 Ala Leu Cys Thr Arg Cys Ile Gln Ile Asn Thr Asp Ser Ser Leu Leu
 625 630 635 640
 Asn Ser Glu Phe Cys Phe Ile Leu Lys Val Pro Phe Glu Ser Glu Asp
 645 650 655

Asn Gln Gly Ile Val Tyr Ala Trp Val Gly Arg Ala Ser Asp Pro Asp
 660 665 670
 Glu Ala Lys Leu Ala Glu Asp Ile Leu Asn Thr Met Phe Asp Thr Ser
 675 680 685
 Tyr Ser Lys Gln Val Ile Asn Glu Gly Glu Glu Pro Glu Asn Phe Phe
 690 695 700
 Trp Val Gly Ile Gly Ala Gln Lys Pro Tyr Asp Asp Asp Ala Glu Tyr
 705 710 715 720
 Met Lys His Thr Arg Leu Phe Arg Cys Ser Asn Glu Lys Gly Tyr Phe
 725 730 735
 Ala Val Thr Glu Lys Cys Ser Asp Phe Cys Gln Asp Asp Leu Ala Asp
 740 745 750
 Asp Asp Ile Met Leu Leu Asp Asn Gly Gln Glu Val Tyr Met Trp Val
 755 760 765
 Gly Thr Gln Thr Ser Gln Val Glu Ile Lys Leu Ser Leu Lys Ala Cys
 770 775 780
 Gln Val Tyr Ile Gln His Met Arg Ser Lys Glu His Glu Arg Pro Arg
 785 790 795 800
 Arg Leu Arg Leu Val Arg Lys Gly Asn Glu Gln His Ala Phe Thr Arg
 805 810 815
 Cys Phe His Ala Trp Ser Ala Phe Cys Lys Ala Leu Ala
 820 825

<210> 603
 <211> 221
 <212> PRT
 <213> Homo sapiens

<400> 603
 Thr Glu Pro Pro Leu Ser Cys Cys Leu Pro Ala Thr Tyr Pro Ala Asp
 1 5 10 15
 Met Gly Thr Ala Gly Ala Met Gln Leu Cys Trp Val Ile Leu Gly Phe
 20 25 30
 Leu Leu Phe Arg Gly His Asn Ser Gln Pro Thr Met Thr Gln Thr Ser
 35 40 45

Ser Ser Gln Gly Gly Leu Gly Gly Leu Ser Leu Thr Thr Glu Pro Val
 50 55 60
 Ser Ser Asn Pro Gly Tyr Ile Pro Ser Ser Glu Ala Asn Arg Pro Ser
 65 70 75 80
 His Leu Ser Ser Thr Gly Thr Pro Gly Ala Gly Val Pro Ser Ser Gly
 85 90 95
 Arg Asp Gly Gly Thr Ser Arg Asp Thr Phe Gln Thr Val Pro Pro Asn
 100 105 110
 Ser Thr Thr Met Ser Leu Ser Met Arg Glu Asp Ala Thr Ile Leu Pro
 115 120 125
 Ser Pro Thr Ser Glu Thr Val Leu Thr Val Ala Ala Phe Gly Val Ile
 130 135 140
 Ser Phe Ile Val Ile Leu Val Val Val Val Ile Ile Leu Val Gly Val
 145 150 155 160
 Val Ser Leu Arg Phe Lys Cys Arg Lys Ser Lys Glu Ser Glu Asp Pro
 165 170 175
 Gln Lys Pro Gly Ser Ser Gly Leu Ser Glu Ser Cys Ser Thr Ala Asn
 180 185 190
 Gly Glu Lys Asp Ser Ile Thr Leu Ile Ser Met Lys Asn Ile Asn Met
 195 200 205
 Asn Asn Gly Lys Gln Ser Leu Ser Ala Glu Lys Val Leu
 210 215 220

<210> 604

<211> 97

<212> PRT

<213> Homo sapiens

<400> 604

Ser Cys Gly Leu Ser Leu Ile Lys Met Thr Thr Ser Gln Lys His Arg
 1 5 10 15
 Asp Phe Val Ala Glu Pro Met Gly Glu Lys Pro Val Gly Ser Leu Ala
 20 25 30
 Gly Ile Gly Glu Val Leu Gly Lys Lys Leu Glu Glu Arg Gly Phe Asp
 35 40 45
 Lys Ala Tyr Val Val Leu Gly Gln Phe Leu Val Leu Lys Lys Asp Glu

564

50 55 60
 Asp Leu Phe Arg Glu Trp Leu Lys Asp Thr Cys Gly Ala Asn Ala Lys
 65 70 75 80
 Gln Ser Arg Asp Cys Phe Gly Cys Leu Arg Glu Trp Cys Asp Ala Phe
 85 90 95

Leu

<210> 605

<211> 266

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 605

Gly Pro Arg Arg Leu Gly Ala Leu His Ala Ala Ala Thr Gly Ala Arg
 1 5 10 15
 Cys Leu Val Glu Leu Leu Val Ala His Gly Ala Asp Leu Asn Ala Lys
 20 25 30
 Ser Leu Met Asp Glu Thr Pro Leu Asp Val Cys Gly Asp Glu Glu Val
 35 40 45
 Arg Ala Lys Leu Leu Glu Leu Lys His Lys His Asp Ala Leu Leu Arg
 50 55 60
 Ala Gln Ser Arg Gln Arg Ser Leu Leu Arg Arg Arg Thr Ser Ser Ala
 65 70 75 80
 Gly Ser Arg Xaa Lys Val Val Arg Arg Val Ser Leu Thr Gln Arg Thr
 85 90 95
 Asp Leu Tyr Arg Lys Gln His Ala Gln Glu Ala Ile Val Trp Gln Gln
 100 105 110
 Pro Pro Pro Thr Ser Pro Glu Pro Pro Glu Asp Asn Asp Asp Arg Gln
 115 120 125
 Thr Gly Ala Glu Leu Arg Pro Pro Pro Pro Glu Glu Asp Asn Pro Glu
 130 135 140

Val Val Arg Pro His Asn Gly Arg Val Gly Gly Ser Pro Val Arg His
 145 150 155 160
 Leu Tyr Ser Lys Arg Leu Asp Arg Ser Val Ser Tyr Gln Leu Ser Pro
 165 170 175
 Leu Asp Ser Thr Thr Pro His Thr Leu Val His Asp Lys Ala His His
 180 185 190
 Thr Leu Ala Asp Leu Lys Arg Gln Arg Ala Ala Ala Lys Leu Gln Arg
 195 200 205
 Pro Pro Pro Glu Gly Pro Glu Ser Pro Glu Thr Ala Glu Pro Gly Leu
 210 215 220
 Pro Gly Asp Thr Val Thr Pro Gln Pro Asp Cys Gly Phe Arg Ala Gly
 225 230 235 240
 Gly Asp Pro Pro Leu Leu Lys Leu Thr Ala Pro Ala Val Glu Ala Pro
 245 250 255
 Val Glu Arg Arg Pro Cys Cys Leu Leu Met
 260 265

<210> 606

<211> 331

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (91)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (285)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 606

His Asp Ser Cys Phe Val Glu Met Gln Ala Gln Lys Val Met His Val
 1 5 10 15

Ser Ser Ala Glu Leu Asn Tyr Ser Leu Pro Tyr Asp Ser Lys His Gln
 20 25 30

Ile Arg Asn Ala Ser Asn Val Lys His His Asp Ser Ser Ala Leu Gly
 35 40 45

Val Tyr Ser Tyr Ile Pro Leu Val Glu Asn Pro Tyr Phe Ser Ser Trp
50 55 60

Pro Pro Ser Gly Thr Ser Ser Lys Met Ser Leu Asp Leu Pro Gln Lys
65 70 75 80

Gln Asp Gly Thr Val Phe Pro Ser Ser Leu Xaa Pro Thr Ser Ser Thr
85 90 95

Ser Leu Phe Ser Tyr Tyr Asn Ser His Asp Ser Leu Ser Leu Asn Ser
100 105 110

Pro Thr Asn Ile Ser Ser Leu Leu Asn Gln Glu Ser Ala Val Leu Ala
115 120 125

Thr Ala Pro Arg Ile Asp Asp Glu Ile Pro Pro Pro Leu Pro Val Arg
130 135 140

Thr Pro Glu Ser Phe Ile Val Val Glu Glu Ala Gly Glu Phe Ser Pro
145 150 155 160

Asn Val Pro Lys Ser Leu Ser Ser Ala Val Lys Val Lys Ile Gly Thr
165 170 175

Ser Leu Glu Trp Gly Gly Thr Ser Glu Pro Lys Lys Phe Asp Asp Ser
180 185 190

Val Ile Leu Arg Pro Ser Lys Ser Val Lys Leu Arg Ser Pro Lys Ser
195 200 205

Glu Leu His Gln Asp Arg Ser Ser Pro Pro Pro Pro Leu Pro Glu Arg
210 215 220

Thr Leu Glu Ser Phe Phe Leu Ala Asp Glu Asp Cys Met Gln Ala Gln
225 230 235 240

Ser Ile Glu Thr Tyr Ser Thr Ser Tyr Pro Asp Thr Met Glu Asn Ser
245 250 255

Thr Ser Ser Lys Gln Thr Leu Lys Thr Pro Gly Lys Ser Phe Thr Arg
260 265 270

Ser Lys Ser Leu Lys Ile Leu Arg Asn Met Lys Lys Xaa Ile Cys Asn
275 280 285

Ser Cys Pro Pro Asn Lys Pro Ala Glu Ser Val Gln Ser Asn Asn Ser
290 295 300

Ser Ser Phe Leu Asn Phe Gly Phe Ala Asn Arg Phe Ser Lys Pro Lys
305 310 315 320

Gly Pro Arg Asn Pro Pro Pro Thr Trp Asn Ile
 325 330

<210> 607

<211> 192

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (78)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 607

Ala Ala Pro Ser Glu Pro Lys Ala Arg Gly Gly His Gly Gly Ala Leu
 1 5 10 15

Ala Arg Leu Glu Thr Met Pro Lys Leu Gln Gly Phe Glu Phe Trp Ser
 20 25 30

Arg Thr Leu Arg Gly Ala Arg His Val Val Ala Pro Met Val Asp Gln
 35 40 45

Ser Glu Leu Ala Trp Arg Leu Leu Ser Arg Arg His Gly Ala Gln Leu
 50 55 60

Cys Tyr Thr Pro Met Leu His Ala Gln Val Phe Val Arg Xaa Ala Asn
 65 70 75 80

Tyr Arg Lys Glu Asn Leu Tyr Cys Glu Val Cys Pro Glu Asp Arg Pro
 85 90 95

Leu Ile Val Gln Phe Cys Ala Asn Asp Pro Glu Val Phe Val Gln Ala
 100 105 110

Ala Leu Leu Ala Gln Asp Tyr Cys Asp Ala Ile Asp Leu Asn Leu Gly
 115 120 125

Cys Pro Gln Met Ile Ala Lys Arg Gly His Tyr Gly Ala Phe Leu Gln
 130 135 140

Asp Glu Trp Asp Leu Leu Gln Arg Met Ile Leu Leu Ala His Glu Lys
 145 150 155 160

Leu Ser Val Pro Val Thr Cys Lys Ile Arg Val Phe Pro Glu Ile Asp
 165 170 175

Lys Thr Val Ser Thr Pro Arg Cys Trp Arg Arg Pro Ala Ala Ser Cys
 180 185 190

<210> 608
<211> 415
<212> PRT
<213> Homo sapiens

<400> 608

His Ile Lys Cys Pro His Ser Lys Tyr Gly Cys Thr Phe Ile Gly Asn
1 5 10 15
Gln Asp Thr Tyr Glu Thr His Leu Glu Thr Cys Arg Phe Glu Gly Leu
20 25 30
Lys Glu Phe Leu Gln Gln Thr Asp Asp Arg Phe His Glu Met His Val
35 40 45
Ala Leu Ala Gln Lys Asp Gln Glu Ile Ala Phe Leu Arg Ser Met Leu
50 55 60
Gly Lys Leu Ser Glu Lys Ile Asp Gln Leu Glu Lys Ser Leu Glu Leu
65 70 75 80
Lys Phe Asp Val Leu Asp Glu Asn Gln Ser Lys Leu Ser Glu Asp Leu
85 90 95
Met Glu Phe Arg Arg Asp Ala Ser Met Leu Asn Asp Glu Leu Ser His
100 105 110
Ile Asn Ala Arg Leu Asn Met Gly Ile Leu Gly Ser Tyr Asp Pro Gln
115 120 125
Gln Ile Phe Lys Cys Lys Gly Thr Phe Val Gly His Gln Gly Pro Val
130 135 140
Trp Cys Leu Cys Val Tyr Ser Met Gly Asp Leu Leu Phe Ser Gly Ser
145 150 155 160
Ser Asp Lys Thr Ile Lys Val Trp Asp Thr Cys Thr Thr Tyr Lys Cys
165 170 175
Gln Lys Thr Leu Glu Gly His Asp Gly Ile Val Leu Ala Leu Cys Ile
180 185 190
Gln Gly Cys Lys Leu Tyr Ser Gly Ser Ala Asp Cys Thr Ile Ile Val
195 200 205

Trp Asp Ile Gln Asn Leu Gln Lys Val Asn Thr Ile Arg Ala His Asp
210 215 220

Asn Pro Val Cys Thr Leu Val Ser Ser His Asn Val Leu Phe Ser Gly
225 230 235 240

Ser Leu Lys Ala Ile Lys Val Trp Asp Ile Val Gly Thr Glu Leu Lys
245 250 255

Leu Lys Lys Glu Leu Thr Gly Leu Asn His Trp Val Arg Ala Leu Val
260 265 270

Ala Ala Gln Ser Tyr Leu Tyr Ser Gly Ser Tyr Gln Thr Ile Lys Ile
275 280 285

Trp Asp Ile Arg Thr Leu Asp Cys Ile His Val Leu Gln Thr Ser Gly
290 295 300

Gly Ser Val Tyr Ser Ile Ala Val Thr Asn His His Ile Val Cys Gly
305 310 315 320

Thr Tyr Glu Asn Leu Ile His Val Trp Asp Ile Glu Ser Lys Glu Gln
325 330 335

Val Arg Thr Leu Thr Gly His Val Gly Thr Val Tyr Ala Leu Ala Val
340 345 350

Ile Ser Thr Pro Asp Gln Thr Lys Val Phe Ser Ala Ser Tyr Asp Arg
355 360 365

Ser Leu Arg Val Trp Ser Met Asp Asn Met Ile Cys Thr Gln Thr Leu
370 375 380

Leu Arg His Gln Gly Ser Val Thr Ala Leu Ala Val Ser Arg Gly Arg
385 390 395 400

Leu Phe Ser Gly Ala Val Asp Ser Thr Val Lys Val Trp Thr Cys
405 410 415

<210> 609

<211> 48

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (27)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (34)
<223> Xaa equals any of the naturally occurring L amino acids

<400> 609
Phe Ser Glu Leu Asn Gln Cys Phe Tyr Ile Cys Phe Phe Phe Tyr Ala
1 5 10 15
Ser Trp Lys Trp Arg Met Lys Ile Gln Leu Xaa Cys Ser Asn Ser Arg
20 25 30
Arg Xaa Val Ser Thr Glu Lys Gly Thr Cys Phe Phe Thr Pro Glu Leu
35 40 45

<210> 610
<211> 241
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (3)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (7)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (13)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (37)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 610

Xaa Asp Xaa Gly Arg Pro Xaa Arg Thr Ala Glu Ser Xaa Phe Gly Ile
1 5 10 15
Asn Leu Lys Gly Pro Lys Ile Lys Gly Gly Ala Asp Val Ser Gly Gly
20 25 30
Val Ser Ala Pro Xaa Ile Ser Leu Gly Glu Gly His Leu Ser Val Lys
35 40 45
Gly Ser Gly Gly Glu Trp Lys Gly Pro Gln Val Ser Ser Ala Leu Asn
50 55 60
Leu Asp Thr Ser Lys Phe Ala Gly Gly Leu His Phe Ser Gly Pro Lys
65 70 75 80
Val Glu Gly Gly Val Lys Gly Gly Gln Ile Gly Leu Gln Ala Pro Gly
85 90 95
Leu Ser Val Ser Gly Pro Gln Gly His Leu Glu Ser Gly Ser Gly Lys
100 105 110
Val Thr Phe Pro Lys Met Lys Ile Pro Lys Phe Thr Phe Ser Gly Arg
115 120 125
Glu Leu Val Gly Arg Glu Met Gly Val Asp Val His Phe Pro Lys Ala
130 135 140
Glu Ala Ser Ile Gln Ala Gly Ala Gly Asp Gly Glu Trp Glu Glu Ser
145 150 155 160
Glu Val Lys Leu Lys Lys Ser Lys Ile Lys Met Pro Lys Phe Asn Phe
165 170 175
Ser Lys Pro Lys Gly Lys Gly Gly Val Thr Gly Ser Pro Glu Ala Ser
180 185 190
Ile Ser Gly Ser Lys Gly Asp Leu Lys Ser Ser Lys Ala Ser Leu Gly
195 200 205
Ser Leu Glu Gly Glu Ala Glu Ala Glu Ala Ser Ser Pro Lys Gly Lys
210 215 220
Phe Ser Leu Phe Lys Ser Lys Lys Pro Arg His Arg Cys Lys Phe Ile
225 230 235 240
Gln

<211> 77

<212> PRT

<213> Homo sapiens

<400> 611

His Tyr Arg Arg Tyr Ala Cys Arg Tyr Arg Ser Gly Ile Pro Gly Ser
1 5 10 15
Thr His Ala Ser Gly Val Ala Asp Gly Gly Gln Val Phe Leu Phe Pro
20 25 30
Glu Thr Gly Ser Val Gln Thr Ala Asn Ala His Arg Trp Pro Arg Gly
35 40 45
Gly Gly Ser Gln Gly Val Trp Val Phe Leu Gly Phe Phe Ser Val Val
50 55 60
Ser Phe Thr Gln Gly Trp Trp Ser Gln Pro Val Trp Cys
65 70 75

<210> 612

<211> 137

<212> PRT

<213> Homo sapiens

<400> 612

Leu Gln Val Pro Val Arg Asn Ser Gly Ser Pro Thr Arg Gln Ala Ala
1 5 10 15
Ala Met Thr Phe Cys Arg Leu Leu Asn Arg Cys Gly Glu Ala Ala Arg
20 25 30
Ser Leu Pro Leu Gly Ala Arg Cys Phe Gly Val Arg Val Ser Pro Thr
35 40 45
Gly Glu Lys Val Thr His Thr Gly Gln Val Tyr Asp Asp Lys Asp Tyr
50 55 60
Arg Arg Ile Arg Phe Val Gly Arg Gln Lys Glu Val Asn Glu Asn Phe
65 70 75 80
Ala Ile Asp Leu Ile Ala Glu Gln Pro Val Ser Glu Val Glu Thr Arg
85 90 95
Val Ile Ala Cys Asp Gly Gly Gly Gly Ala Leu Gly His Pro Lys Val
100 105 110
Tyr Ile Asn Leu Asp Lys Glu Thr Lys Thr Gly Thr Cys Gly Tyr Cys
115 120 125

Gly Leu Gln Phe Arg Gln His His His
130 135

<210> 613
<211> 122
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (50)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (75)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (80)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (85)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (98)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (105)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (111)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (116)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 613

Tyr Ser Thr Asp Asn Asn Asn Asn Trp Tyr Ser Ile Phe Tyr Leu His
1 5 10 15
Ser Ser Phe Leu Gly Glu Asn Ala Glu Lys Leu Leu Gln Phe Lys Arg
20 25 30
Trp Phe Trp Ser Ile Val Glu Lys Met Ser Met Thr Glu Arg Gln Asp
35 40 45
Leu Xaa Tyr Phe Trp Thr Ser Ser Pro Ser Leu Pro Ala Ser Glu Glu
50 55 60
Gly Phe Gln Pro Met Pro Ser Ile Thr Ile Xaa Pro Pro Asp Asp Xaa
65 70 75 80
His Leu Pro Thr Xaa Lys Tyr Leu His Phe Leu Asp Phe Thr Phe Pro
85 90 95
Leu Xaa Ser Phe Lys Gln Asp Ser Xaa Asn Arg Lys Leu Val Xaa Ser
100 105 110
Pro Phe Arg Xaa Gln Lys Phe Trp Val Leu
115 120

<210> 614

<211> 62

<212> PRT

<213> Homo sapiens

<400> 614

Phe Phe Ile Gly Leu Glu Thr Arg Ala Asn Ser Ile Met Phe Ser Lys
1 5 10 15
Glu Thr Asp Leu Ser Cys Trp Ile Arg Gly Thr Asn Pro Thr Tyr Met
20 25 30
Ile Phe Phe Leu Phe Leu Ser Cys Ser Tyr Gly Thr Val Leu Phe Gly
35 40 45
Thr Phe Ala Thr Arg Asp Asn Thr Thr Phe Leu Thr Leu Ile
50 55 60

<210> 615

<211> 159

<212> PRT

<213> Homo sapiens

575

<400> 615

Val Gly Leu Pro Asn Met Ala Gln Ser Ile Asn Ile Thr Glu Leu Asn
 1 5 10 15

Leu Pro Gln Leu Glu Met Leu Lys Asn Gln Leu Asp Gln Glu Val Glu
 20 25 30

Phe Leu Ser Thr Ser Ile Ala Gln Leu Lys Val Val Gln Thr Lys Tyr
 35 40 45

Val Glu Ala Lys Asp Cys Leu Asn Val Leu Asn Lys Ser Asn Glu Gly
 50 55 60

Lys Glu Leu Leu Val Pro Leu Thr Ser Ser Met Tyr Val Pro Gly Lys
 65 70 75 80

Leu His Asp Val Glu His Val Leu Ile Asp Val Gly Thr Gly Tyr Tyr
 85 90 95

Val Glu Lys Thr Ala Glu Asp Ala Lys Asp Phe Phe Lys Arg Lys Ile
 100 105 110

Asp Phe Leu Thr Lys Gln Met Glu Lys Ile Gln Pro Ala Leu Gln Glu
 115 120 125

Lys His Ala Met Lys Gln Ala Val Met Glu Met Met Ser Gln Lys Ile
 130 135 140

Gln Gln Leu Thr Ala Leu Gly Ala Ala Gln Ala Thr Ala Lys Ala
 145 150 155

<210> 616

<211> 93

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (8)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 616

Lys Val Ala Cys Arg Tyr Arg Xaa Gly Ile Pro Gly Arg Pro Thr Arg
 1 5 10 15

Pro Gly Thr Gln Asp Ala Glu Gly Lys Lys Ala Lys Gly Lys Lys Val
 20 25 30

Ala Pro Ala Pro Ala Val Val Lys Lys Gln Glu Ala Lys Lys Val Val
 35 40 45

Asn Pro Leu Phe Glu Lys Arg Pro Lys Asn Phe Gly Ile Gly Gln Asp
 50 55 60

Ile Gln Pro Lys Arg Asp Leu Thr Arg Phe Val Lys Trp Pro Arg Tyr
 65 70 75 80

Ile Arg Leu Gln Arg His Ala Arg Ser Ser Thr Ser Gly
 85 90

<210> 617

<211> 362

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (307)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 617

Ser Arg Val Asp Pro Arg Val Arg Arg Gly Val Pro Tyr Gln Leu Gly
 1 5 10 15

Pro His Gly His Arg Gln Gly Leu Glu Ala Pro Leu Tyr Leu Thr Pro
 20 25 30

Glu Gly Trp Ser Leu Phe Leu Gln Arg Tyr Tyr Gln Val Val His Glu
 35 40 45

Gly Ala Glu Leu Arg His Leu Asp Thr Gln Val Gln Arg Cys Glu Asp
 50 55 60

Ile Leu Gln Gln Leu Gln Ala Val Val Pro Gln Ile Asp Met Glu Gly
 65 70 75 80

Asp Arg Asn Ile Trp Ile Val Lys Pro Gly Ala Lys Ser Arg Gly Arg
 85 90 95

Gly Ile Met Cys Met Asp His Leu Glu Glu Met Leu Lys Leu Val Asn
 100 105 110

Gly Asn Pro Val Val Met Lys Asp Gly Lys Trp Val Val Gln Lys Tyr
 115 120 125

Ile Glu Arg Pro Leu Leu Ile Phe Gly Thr Lys Phe Asp Leu Arg Gln
 130 135 140

Trp Phe Leu Val Thr Asp Trp Asn Pro Leu Thr Val Trp Phe Tyr Arg
145 150 155 160

Asp Ser Tyr Ile Arg Phe Ser Thr Gln Pro Phe Ser Leu Lys Asn Leu
165 170 175

Asp Asn Ser Val His Leu Cys Asn Asn Ser Ile Gln Lys His Leu Glu
180 185 190

Asn Ser Cys His Arg His Pro Leu Leu Pro Pro Asp Asn Met Trp Ser
195 200 205

Ser Gln Arg Phe Gln Ala His Leu Gln Glu Met Gly Ala Pro Asn Ala
210 215 220

Trp Ser Thr Ile Ile Val Pro Gly Met Lys Asp Ala Val Ile His Ala
225 230 235 240

Leu Gln Thr Ser Gln Asp Thr Val Gln Cys Arg Lys Ala Ser Phe Glu
245 250 255

Leu Tyr Gly Ala Asp Phe Val Phe Gly Glu Asp Phe Gln Pro Trp Leu
260 265 270

Ile Glu Ile Asn Ala Ser Pro Thr Met Ala Pro Ser Thr Ala Val Thr
275 280 285

Ala Arg Leu Cys Ala Gly Val Gln Ala Asp Thr Leu Arg Val Val Ile
290 295 300

Asp Arg Xaa Leu Asp Arg Asn Cys Asp Thr Gly Ala Phe Glu Leu Ile
305 310 315 320

Tyr Lys Gln Pro Ala Val Glu Val Pro Gln Tyr Val Gly Ile Arg Leu
325 330 335

Leu Val Glu Gly Phe Thr Ile Lys Lys Pro Met Ala Met Cys His Arg
340 345 350

Arg Met Gly Val Arg Gln Gln Ser Leu Cys
355 360

<210> 618

<211> 328

<212> PRT

<213> Homo sapiens

<400> 618

Ile Arg Met Arg Glu Trp Trp Val Gln Val Gly Leu Leu Ala Val Pro
 1 5 10 15
 Leu Leu Ala Ala Tyr Leu His Ile Pro Pro Pro Gln Leu Ser Pro Ala
 20 25 30
 Leu His Ser Trp Lys Ser Ser Gly Lys Phe Phe Thr Tyr Lys Gly Leu
 35 40 45
 Arg Ile Phe Tyr Gln Asp Ser Val Gly Val Val Gly Ser Pro Glu Ile
 50 55 60
 Val Val Leu Leu His Gly Phe Pro Thr Ser Ser Tyr Asp Trp Tyr Lys
 65 70 75 80
 Ile Trp Glu Gly Leu Thr Leu Arg Phe His Arg Val Ile Ala Leu Asp
 85 90 95
 Phe Leu Gly Phe Gly Phe Ser Asp Lys Pro Arg Pro His His Tyr Ser
 100 105 110
 Ile Phe Glu Gln Ala Ser Ile Val Glu Ala Leu Leu Arg His Leu Gly
 115 120 125
 Leu Gln Asn Arg Arg Ile Asn Leu Leu Ser His Asp Tyr Gly Asp Ile
 130 135 140
 Val Ala Gln Glu Leu Leu Tyr Arg Tyr Lys Gln Asn Arg Ser Gly Arg
 145 150 155 160
 Leu Thr Ile Lys Ser Leu Cys Leu Ser Asn Gly Gly Ile Phe Pro Glu
 165 170 175
 Thr His Arg Pro Leu Leu Leu Gln Lys Leu Leu Lys Asp Gly Gly Val
 180 185 190
 Leu Ser Pro Ile Leu Thr Arg Leu Met Asn Phe Phe Val Phe Ser Arg
 195 200 205
 Gly Leu Thr Pro Val Phe Gly Pro Tyr Thr Arg Pro Ser Glu Ser Glu
 210 215 220
 Leu Trp Asp Met Trp Ala Gly Ile Arg Asn Asn Asp Gly Asn Leu Val
 225 230 235 240
 Ile Asp Ser Leu Leu Gln Tyr Ile Asn Gln Arg Lys Lys Phe Arg Arg
 245 250 255
 Arg Trp Val Gly Ala Leu Ala Ser Val Thr Ile Pro Ile His Phe Ile
 260 265 270

Tyr Gly Pro Leu Asp Pro Val Asn Pro Tyr Pro Glu Phe Leu Glu Leu
275 280 285

Tyr Arg Lys Thr Leu Pro Arg Ser Thr Val Ser Ile Leu Asp Asp His
290 295 300

Ile Ser His Tyr Pro Gln Leu Glu Asp Pro Met Gly Phe Leu Asn Ala
305 310 315 320

Tyr Met Gly Phe Ile Asn Ser Phe
325

<210> 619

<211> 271

<212> PRT

<213> Homo sapiens

<400> 619

Asn Met Asp Pro Pro Gly Leu Gln Gly Val Gln Gly Thr Val Ala Ala
1 5 10 15

Cys Gly Ala Cys Tyr Trp Leu Leu Gly Leu Met Ala Val Arg Ala Ser
20 25 30

Phe Glu Asn Asn Cys Glu Ile Gly Cys Phe Ala Lys Leu Thr Asn Thr
35 40 45

Tyr Cys Leu Val Ala Ile Gly Gly Ser Glu Asn Phe Tyr Ser Val Phe
50 55 60

Glu Gly Glu Leu Ser Asp Thr Ile Pro Val Val His Ala Ser Ile Ala
65 70 75 80

Gly Cys Arg Ile Ile Gly Arg Met Cys Val Gly Asn Arg His Gly Leu
85 90 95

Leu Val Pro Asn Asn Thr Thr Asp Gln Glu Leu Gln His Ile Arg Asn
100 105 110

Ser Leu Pro Asp Thr Val Gln Ile Arg Arg Val Glu Glu Arg Leu Ser
115 120 125

Ala Leu Gly Asn Val Thr Thr Cys Asn Asp Tyr Val Ala Leu Val His
130 135 140

Pro Asp Leu Asp Arg Glu Thr Glu Glu Ile Leu Ala Asp Val Leu Lys
145 150 155 160

Val Glu Val Phe Arg Gln Thr Val Ala Asp Gln Val Leu Val Gly Ser

580

| | | |
|---|-----|-----|
| 165 | 170 | 175 |
| Tyr Cys Val Phe Ser Asn Gln Gly Gly Leu Val His Pro Lys Thr Ser | | |
| 180 | 185 | 190 |
| Ile Glu Asp Gln Asp Glu Leu Ser Ser Leu Leu Gln Val Pro Leu Val | | |
| 195 | 200 | 205 |
| Ala Gly Thr Val Asn Arg Gly Ser Glu Val Ile Ala Ala Gly Met Val | | |
| 210 | 215 | 220 |
| Val Asn Asp Trp Cys Ala Phe Cys Gly Leu Asp Thr Thr Ser Thr Glu | | |
| 225 | 230 | 235 |
| Leu Ser Val Val Glu Ser Val Phe Lys Leu Asn Glu Ala Gln Pro Ser | | |
| 245 | 250 | 255 |
| Thr Ile Ala Thr Ser Met Arg Asp Ser Leu Ile Asp Ser Leu Thr | | |
| 260 | 265 | 270 |

<210> 620

<211> 88

<212> PRT

<213> Homo sapiens

<400> 620

| | | |
|---|----|----|
| Gly Ser Ala Ala Met Lys Val Lys Ile Lys Cys Trp Asn Gly Val Ala | | |
| 1 | 5 | 10 |
| Thr Trp Leu Trp Val Ala Asn Asp Glu Asn Cys Gly Ile Cys Arg Met | | |
| 20 | 25 | 30 |
| Ala Phe Asn Gly Cys Cys Pro Asp Cys Lys Val Pro Gly Asp Asp Cys | | |
| 35 | 40 | 45 |
| Pro Leu Val Trp Gly Gln Cys Ser His Cys Phe His Met His Cys Ile | | |
| 50 | 55 | 60 |
| Leu Lys Trp Leu His Ala Gln Gln Val Gln Gln His Cys Pro Met Cys | | |
| 65 | 70 | 75 |
| Arg Gln Glu Trp Lys Phe Lys Glu | | |
| 85 | | |

<210> 621

<211> 46

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (41)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 621

Ala Gly Thr Ser Arg Ser Glu Gly Lys Arg Ser Ser Val Leu Thr Arg
1 5 10 15

Thr Glu Phe Gln Ile Glu Met Phe Gln Thr Ile Glu Gly Glu Lys Trp
20 25 30

Pro Gly Xaa Ser Ile Asn Leu Ser Xaa Phe His Gly Cys Phe
35 40 45

<210> 622

<211> 103

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 622

Gly Arg Pro Thr Arg Pro Arg Gly Arg Gly Arg Ser Ser Ala Cys Leu
1 5 10 15

Leu Leu Glu Gly Asp Gly Pro Ala Arg Leu Trp Ala Pro Thr Ser Pro
20 25 30

Gly Val Xaa Xaa Glu Arg Phe Ala Glu Glu Arg Gly Ser Gly Arg Ala
35 40 45

Leu Asn Ala Gly Pro Lys His Pro Gly Ser Leu His Ser Pro Arg Pro
50 55 60

Gln Thr Leu Thr Lys Thr Trp Ile Cys Ser Arg Phe Ser Cys Ser Arg
 65 70 75 80
 Ser Ser Arg Ser Cys Pro Arg Leu Leu Arg Leu Arg Ala Glu Lys Lys
 85 90 95
 Val Cys Gln Ala Trp Thr Gln
 100

<210> 623

<211> 103

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (60)

<223> Xaa equals any of the naturally occurring-L-amino acids

<400> 623

Gly Arg Pro Thr Arg Pro Thr Ser Ser Arg Ser Arg Ala Ala Arg Pro
 1 5 10 15
 Phe Phe Phe Phe Phe Phe Trp Phe Pro Glu Phe Gly Phe Ile Leu
 20 25 30
 Gln Tyr Arg Asn His Leu Glu Pro Ser Glu Thr Asp Ile Pro Glu Ala
 35 40 45
 Glu Ala Leu Ser Asn Gln Tyr Cys Val Ala Leu Xaa Pro Leu Arg Lys
 50 55 60
 Pro His Leu Gly Tyr Lys Arg Ser Phe Tyr Val Tyr Pro Leu Tyr His
 65 70 75 80
 Gly Phe Leu Ser Pro Leu Leu Leu Pro Ile Leu Pro Gly Glu Asn Thr
 85 90 95
 Ala Gln Arg Leu Pro Ser Glu
 100

<210> 624

<211> 305

<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (116)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (117)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (219)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 624
Thr Gln Asp Leu Trp Met Ser Cys Pro Val Gln Thr Met Asp Pro Glu
1 5 10 15
Val Thr Leu Leu Leu Gln Cys Pro Gly Gly Gly Leu Pro Gln Glu Gln
20 25 30
Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg Pro Leu Pro Gly
35 40 45
Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg Leu Lys Ala Gln
50 55 60
Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His Ser Ala Thr Leu
65 70 75 80
Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu Arg Leu Gly Leu
85 90 95
Thr Ser Tyr Arg Asp Phe Leu Gly Thr Asn Trp Ser Ser Ser Ala Ala
100 105 110
Trp Leu Arg Xaa Xaa Gly Ala Thr Asp Trp Gly Asp Thr Gln Ala Tyr
115 120 125
Leu Ala Asp Pro Leu Gly Val Gly Ala Ala Leu Ala Thr Ala Asp Asp
130 135 140
Phe Leu Val Phe Leu Arg Ser Arg Gln Val Ala Glu Ala Pro Gly
145 150 155 160
Leu Val Asp Val Pro Gly Gly His Pro Glu Pro Gln Ala Leu Cys Pro
165 170 175
Gly Gly Ser Pro Gln His Gln Asp Leu Ala Gly Gln Leu Val Val His
180 185 190

Glu Leu Phe Ser Ser Val Leu Gln Glu Ile Cys Asp Glu Val Asn Leu
 195 200 205
 Pro Leu Leu Thr Leu Ser Gln Pro Leu Leu Xaa Gly Ile Ala Arg Asn
 210 215 220
 Glu Thr Ser Ala Gly Arg Ala Ser Ala Glu Phe Tyr Val Gln Cys Ser
 225 230 235 240
 Leu Thr Ser Glu Gln Val Arg Lys His Tyr Leu Ser Gly Gly Pro Glu
 245 250 255
 Ala His Glu Ser Thr Gly Ile Phe Phe Val Glu Thr Gln Asn Val Arg
 260 265 270
 Arg Leu Pro Glu Thr Glu Met Trp Ala Glu Leu Cys Pro Ser Pro Lys
 275 280 285
 Ala Pro Ser Ser Ser Thr Thr Gly Phe Arg Glu Val Pro Leu Glu Arg
 290 295 300
 Pro
 305

<210> 625
 <211> 102
 <212> PRT
 <213> Homo sapiens

<400> 625
 Ser Ala Met Lys Ala Ser Gly Thr Leu Arg Glu Tyr Lys Val Val Gly
 1 5 10 15
 Arg Cys Leu Pro Thr Pro Lys Cys Arg Thr Pro Pro Leu Tyr Arg Met
 20 25 30
 Arg Ile Phe Ala Pro Asn His Val Val Ala Lys Ser Arg Phe Trp Tyr
 35 40 45
 Phe Val Ser Gln Leu Lys Lys Met Lys Lys Ser Ser Gly Glu Ile Val
 50 55 60
 Tyr Cys Gly Gln Val Phe Glu Lys Ser Pro Leu Arg Val Lys Asn Phe
 65 70 75 80
 Gly Ile Trp Leu Arg Tyr Asp Ser Arg Ser Gly Thr His Asn Met Tyr
 85 90 95

Arg Gly Val Pro Gly Thr
100

<210> 626

<211> 59

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 626

Ala Leu Trp Val Lys Ala Trp Arg Gln Glu Ser Glu Gly Gln Phe Gln
1 5 10 15

Glu Thr Gln Phe Ile Asn Phe His Gln His Leu Pro Gly Pro Cys Leu
20 25 30

Gly Thr Glu Xaa Pro Ser Pro Glu Ser Gly His His Phe Pro Phe Gln
35 40 45

Ser Ile Glu Cys Arg Gly Ile Gln Gly Met Gly
50 55

<210> 627

<211> 220

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (93)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 627

Arg Leu Val Val Thr Glu Glu Asp Gly Gly Ala Arg Pro Glu Ala Leu
1 5 10 15

Gly Lys Ile Ala Pro Arg Thr Pro Ala Glu Leu Gly Ala Arg Ala Asp
20 25 30

Gln Glu Leu Val Thr Ala Leu Met Cys Asp Leu Arg Arg Pro Ala Ala
35 40 45

Gly Gly Met Met Asp Leu Ala Tyr Val Cys Glu Trp Glu Lys Trp Ser

50 55 60
 Lys Ser Thr His Cys Pro Ser Val Pro Leu Ala Cys Ala Trp Ser Cys
 65 70 75 80
 Arg Asn Leu Ile Ala Phe Thr Met Asp Leu Arg Thr Xaa Asp Gln Asp
 85 90 95
 Leu Thr Arg Met Ile His Ile Leu Asp Thr Glu His Pro Trp Asp Leu
 100 105 110
 His Ser Ile Pro Ser Glu His His Glu Ala Ile Thr Cys Leu Glu Trp
 115 120 125
 Asp Gln Ser Gly Ser Arg Leu Leu Ser Ala Asp Ala Asp Gly Gln Ile
 130 135 140
 Lys Cys Trp Ser Met Ala Asp His Leu Ala Asn Ser Trp Glu Ser Ser
 145 150 155 160
 Val Gly Ser Leu Val Glu Gly Asp Pro Ile Val Ala Leu Ser Trp Leu
 165 170 175
 His Asn Gly Val Lys Leu Ala Leu His Val Glu Lys Ser Gly Ala Ser
 180 185 190
 Ser Phe Gly Glu Lys Phe Ser Arg Val Lys Phe Ser Pro Val Leu Thr
 195 200 205
 Leu Phe Gly Gly Lys Pro Trp Arg Ala Gly Ser Arg
 210 215 220

<210> 628

<211> 119

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (115)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (117)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 628

Pro Ala Ser Val Glu Val Tyr His Asp Ser Leu Cys Arg Lys Ile Trp

587

1 5 10 15
 Arg Glu Asp Asp Lys Trp His Val Ile Phe Arg Ala Asp Gly Trp Glu
 20 25 30
 Gln His Ile Thr Ala Arg Tyr Leu Val Gly Ala Asp Gly Ala Asn Ser
 35 40 45
 Met Val Arg Arg His Leu Tyr Pro Asp His Gln Ile Arg Lys Tyr Val
 50 55 60
 Ala Ile Gln Gln Trp Phe Ala Glu Lys His Pro Val Pro Phe Tyr Ser
 65 70 75 80
 Cys Ile Phe Asp Asn Ser Ile Thr Asn Cys Tyr Ser Trp Ser Ile Ser
 85 90 95
 Lys Asp Gly Tyr Phe Ile Phe Gly Gly Ala Tyr Pro Met Glu Arg Arg
 100 105 110
 Ser Asp Xaa Phe Xaa Asp Ala
 115

<210> 629

<211> 39

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (30)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (31)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 629

Phe Gly Glu Pro Ser Leu Thr Val Arg Ala Asp Ile Thr Gly Arg Tyr
 1 5 10 15
 Ser Ile Val Ser Met Leu Thr Thr Cys Arg Tyr Ser Leu Xaa Xaa His
 20 25 30
 Met Lys Lys Val Ser Ser Cys
 35

588

<210> 630

<211> 267

<212> PRT

<213> Homo sapiens

<400> 630

Ser Ala Ala Leu Pro Gln Pro Thr Pro Pro Leu Thr Leu Pro Gln Ser
1 5 10 15

Met Val Asn Thr Lys Pro Glu Lys Thr Glu Glu Asp Ser Glu Glu Val
20 25 30

Arg Glu Gln Lys His Lys Thr Phe Val Glu Lys Tyr Glu Lys Gln Ile
35 40 45

Lys His Phe Gly Met Leu Arg Arg Trp Asp Asp Ser Gln Lys Tyr Leu
50 55 60

Ser Asp Asn Val His Leu Val Cys Glu Glu Thr Ala Asn Tyr Leu Val
65 70 75 80

Ile Trp Cys Ile Asp Leu Glu Val Glu Glu Lys Cys Ala Leu Met Glu
85 90 95

Gln Val Ala His Gln Thr Ile Val Met Gln Phe Ile Leu Glu Leu Ala
100 105 110

Lys Ser Leu Lys Val Asp Pro Arg Ala Cys Phe Arg Gln Phe Phe Thr
115 120 125

Lys Ile Lys Thr Ala Asp Arg Gln Tyr Met Glu Gly Phe Asn Asp Glu
130 135 140

Leu Glu Ala Phe Lys Glu Arg Val Arg Gly Arg Ala Lys Leu Arg Ile
145 150 155 160

Glu Lys Ala Met Lys Glu Tyr Glu Glu Glu Glu Arg Lys Lys Arg Leu
165 170 175

Gly Pro Gly Gly Leu Asp Pro Val Glu Val Tyr Glu Ser Leu Pro Glu
180 185 190

Glu Leu Gln Lys Cys Phe Asp Val Lys Asp Val Gln Met Leu Gln Asp
195 200 205

Ala Ile Ser Lys Met Asp Pro Thr Asp Ala Lys Tyr His Met Gln Arg
210 215 220

Cys Ile Asp Ser Gly Leu Trp Val Pro Asn Ser Lys Ala Ser Glu Ala
225 230 235 240

589

Lys Glu Gly Glu Glu Ala Gly Pro Gly Asp Pro Leu Leu Glu Ala Val
 245 250 255

Pro Lys Thr Gly Asp Glu Lys Asp Val Ser Val
 260 265

<210> 631

<211> 207

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (164)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 631

Pro Thr Gly Thr Gly Ser Gly Val Pro Gly Leu Gly Arg Asn Gly Gly
 1 5 10 15

Arg Glu Gly Ala Pro Gly Thr Met Gly Leu Leu Thr Ile Leu Lys Lys
 20 25 30

Met Lys Gln Lys Glu Arg Glu Leu Arg Leu Leu Met Leu Gly Leu Asp
 35 40 45

Asn Ala Gly Lys Thr Thr Ile Leu Lys Lys Phe Asn Gly Glu Asp Ile
 50 55 60

Asp Thr Ile Ser Pro Thr Leu Gly Phe Asn Ile Lys Thr Leu Glu His
 65 70 75 80

Arg Gly Phe Lys Leu Asn Ile Trp Asp Val Gly Gly Gln Lys Ser Leu
 85 90 95

Arg Ser Tyr Trp Arg Asn Tyr Phe Glu Ser Thr Asp Gly Leu Ile Trp
 100 105 110

Val Val Asp Ser Ala Asp Arg Gln Arg Met Gln Asp Cys Gln Arg Glu
 115 120 125

Leu Gln Ser Leu Leu Val Glu Glu Arg Leu Ala Gly Ala Thr Leu Leu
 130 135 140

Ile Phe Ala Asn Lys Gln Asp Leu Pro Gly Ala Leu Ser Ser Asn Ala
 145 150 155 160

Ile Arg Glu Xaa Leu Glu Leu Asp Ser Ile Arg Ser His His Trp Cys

590

165 170 175
Ile Gln Gly Cys Ser Ala Val Thr Gly Glu Asn Leu Leu Pro Gly Ile
180 185 190

Asp Trp Leu Leu Asp Asp Ile Ser Ser Arg Ile Phe Thr Ala Asp
195 200 205

<210> 632

<211> 79

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (54)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (60)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (61)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (73)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 632

Lys Asn Asn Lys Lys Asp Gln Gln Asn Gly Ile Cys Ser His Thr Met
1 5 10 15

Ile Lys Thr Tyr Leu Arg Thr Ala Leu Phe Met Gly Lys Arg Ser Leu
20 25 30

Ile Asp Ser Gln Phe His Arg Leu Tyr Arg Arg His Gly Leu Gly Arg
35 40 45

Pro Gln Gly Asn Leu Xaa Ser Met Val Glu Gly Xaa Xaa Gly Ser Met
50 55 60

His His Leu His Trp Pro Glu Gln Xaa Glu Arg Glu Gln Ile Trp
65 70 75

591

<210> 633
<211> 293
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (249)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (282)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 633
Trp Ser Pro Ser Pro Pro Ala Thr Pro Glu Gln Gly Leu Ser Ala Phe
1 5 10 15
Tyr Leu Ser Tyr Phe Asp Met Leu Tyr Pro Glu Asp Ser Ser Trp Ala
20 25 30
Ala Lys Ala Pro Gly Ala Ser Ser Arg Glu Glu Pro Pro Glu Glu Pro
35 40 45
Glu Gln Cys Pro Val Ile Asp Ser Gln Ala Pro Ala Gly Ser Leu Asp
50 55 60
Leu Val Pro Gly Gly Leu Thr Leu Glu Glu His Ser Leu Glu Gln Val
65 70 75 80
Gln Ser Met Val Val Gly Glu Val Leu Lys Asp Ile Glu Thr Ala Cys
85 90 95
Lys Leu Leu Asn Ile Thr Ala Asp Pro Met Asp Trp Ser Pro Ser Asn
100 105 110
Val Gln Lys Trp Leu Leu Trp Thr Glu His Gln Tyr Arg Leu Pro Pro
115 120 125
Met Gly Lys Ala Phe Gln Glu Leu Ala Gly Lys Glu Leu Cys Ala Met
130 135 140
Ser Glu Glu Gln Phe Arg Gln Arg Ser Pro Leu Gly Gly Asp Val Leu
145 150 155 160
His Ala His Leu Asp Ile Trp Lys Ser Ala Ala Trp Met Lys Glu Arg
165 170 175

Thr Ser Pro Gly Ala Ile His Tyr Cys Ala Ser Thr Ser Glu Glu Ser
 180 185 190
 Trp Thr Asp Ser Glu Val Asp Ser Ser Cys Ser Gly Gln Pro Ile His
 195 200 205
 Leu Trp Gln Phe Leu Lys Glu Leu Leu Leu Lys Pro His Ser Tyr Gly
 210 215 220
 Arg Phe Ile Arg Trp Leu Asn Lys Glu Lys Gly Ile Phe Lys Ile Glu
 225 230 235 240
 Asp Ser Ala Gln Val Ala Arg Leu Xaa Gly Ile Arg Lys Asn Arg Pro
 245 250 255
 Ala Met Asn Tyr Asp Lys Leu Ser Arg Ser Ile Arg Gln Tyr Tyr Lys
 260 265 270
 Lys Gly Ile Ile Arg Lys Pro Asp Ile Xaa Gln Arg Leu Val Tyr Gln
 275 280 285
 Phe Val His Pro Ile
 290

<210> 634
 <211> 227
 <212> PRT
 <213> Homo sapiens

<400> 634
 Pro Ala Gly Thr Gly Pro Glu Phe Pro Gly Arg Pro Thr Arg Pro Ala
 1 5 10 15
 Glu Glu Glu Glu Glu Glu Asp Glu Glu Glu Glu Glu Glu Glu
 20 25 30
 Glu Glu Glu Glu Glu Pro Gln Gln Arg Gly Gln Gly Glu Lys Ser Ala
 35 40 45
 Thr Pro Ser Arg Lys Ile Leu Asp Pro Asn Thr Gly Glu Pro Ala Pro
 50 55 60
 Val Leu Ser Ser Pro Pro Pro Ala Asp Val Ser Thr Phe Leu Ala Phe
 65 70 75 80
 Pro Ser Pro Glu Lys Leu Leu Arg Leu Gly Pro Lys Ser Ser Val Leu
 85 90 95
 Ile Ala Gln Gln Thr Asp Thr Ser Asp Pro Glu Lys Val Val Ser Ala

593

100 105 110
 Phe Leu Lys Val Ser Ser Val Phe Lys Asp Glu Ala Thr Val Arg Met
 115 120 125
 Ala Val Gln Asp Ala Val Asp Ala Leu Met Gln Lys Ala Phe Asn Ser
 130 135 140
 Ser Ser Phe Asn Ser Asn Thr Phe Leu Thr Arg Leu Leu Val His Met
 145 150 155 160
 Gly Leu Leu Lys Ser Glu Asp Lys Val Lys Ala Ile Ala Asn Leu Tyr
 165 170 175
 Gly Pro Leu Met Ala Leu Asn His Met Val Gln Gln Asp Tyr Phe Pro
 180 185 190
 Lys Ala Leu Ala Pro Leu Leu Leu Ala Phe Val Thr Lys Pro Asn Ser
 195 200 205
 Ala Leu Glu Ser Cys Ser Phe Ala Arg His Ser Leu Leu Gln Thr Leu
 210 215 220
 Tyr Lys Val
 225

<210> 635
 <211> 126
 <212> PRT
 <213> Homo sapiens

<400> 635
 Thr Ser Gly Cys Ile Ser Asn Gly Lys Met Ser Ser Asn Val Pro Ala
 1 5 10 15
 Asp Met Ile Asn Leu Arg Leu Ile Leu Val Ser Gly Lys Thr Lys Glu
 20 25 30
 Phe Leu Phe Ser Pro Asn Asp Ser Ala Ser Asp Ile Ala Lys His Val
 35 40 45
 Tyr Asp Asn Trp Pro Met Asp Trp Glu Glu Glu Gln Val Ser Ser Pro
 50 55 60
 Asn Ile Leu Arg Leu Ile Tyr Gln Gly Arg Phe Leu His Gly Asn Val
 65 70 75 80
 Thr Leu Gly Ala Leu Lys Leu Pro Phe Gly Lys Thr Thr Val Met His
 85 90 95

594

Leu Val Ala Arg Glu Thr Leu Pro Glu Pro Asn Ser Gln Gly Gln Arg
 100 105 110

Asn Arg Glu Lys Thr Gly Glu Ser Asn Cys Cys Val Ile Leu
 115 120 125

<210> 636

<211> 195

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (96)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 636

Val Ser Gly Phe Ala Gly Pro Ala Ser Leu Ile Ser Met Lys Leu Leu
 1 5 10 15

Ser Leu Val Ala Val Val Gly Cys Leu Leu Val Pro Pro Ala Glu Ala
 20 25 30

Asn Lys Ser Ser Glu Asp Ile Arg Cys Lys Cys Ile Cys Pro Pro Tyr
 35 40 45

Arg Asn Ile Ser Gly His Ile Tyr Asn Gln Asn Val Ser Gln Lys Asp
 50 55 60

Cys Asn Cys Leu His Val Val Glu Pro Met Pro Val Pro Gly His Asp
 65 70 75 80

Val Glu Ala Tyr Cys Leu Leu Cys Glu Cys Arg Tyr Glu Glu Arg Xaa
 85 90 95

Thr Thr Thr Ile Lys Val Ile Ile Val Ile Tyr Leu Ser Val Val Gly
 100 105 110

Ala Leu Leu Leu Tyr Met Ala Phe Leu Met Leu Val Asp Pro Leu Ile
 115 120 125

Arg Lys Pro Asp Ala Tyr Thr Glu Gln Leu His Asn Glu Glu Glu Asn
 130 135 140

Glu Asp Ala Arg Ser Met Ala Ala Ala Ala Ala Ser Leu Gly Gly Pro
 145 150 155 160

Arg Ala Asn Thr Val Leu Glu Arg Val Glu Gly Ala Gln Gln Arg Trp

595

165 170 175
 Lys Leu Gln Val Gln Glu Gln Arg Lys Thr Val Phe Asp Arg His Lys
 180 185 190

Met Leu Ser
 195

<210> 637
 <211> 159
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (92)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (115)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (138)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (151)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (156)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 637
 Arg Pro Thr Arg Pro Gly Asn Ser Arg Arg Arg Gly Arg Arg Gly Cys
 1 5 10 15

Trp Arg Leu Leu Gly Phe Gly Ala Ala Ile Met Pro Gly Ile Val
 20 25 30

Glu Leu Pro Thr Leu Glu Asp Leu Lys Val Gln Glu Val Lys Val Ser
 35 40 45

Ser Ser Val Leu Lys Ala Ala Ala His His Tyr Gly Val Gln Cys Asp

596

50 55 60
 Lys Pro Asn Lys Glu Phe Met Leu Cys Arg Trp Glu Glu Lys Asp Pro
 65 70 75 80
 Arg Arg Cys Leu Glu Glu Gly Lys Leu Val Asn Xaa Cys Ala Leu Asp
 85 90 95
 Phe Phe Arg Gln Ile Lys Leu Ser Leu Cys Arg Ala Phe Tyr Arg Leu
 100 105 110
 Leu Asp Xaa His Arg Leu Leu Arg Pro Ala Val Phe Ser Ser Leu Pro
 115 120 125
 Gln Thr Ala Gly Gln Phe Asp Asp Val Xaa Gly Ala Thr Gly Met Val
 130 135 140
 Arg Leu Asn Trp Gly Lys Xaa Ser Ser His Gln Xaa Glu Asn Ser
 145 150 155

<210> 638
 <211> 20
 <212> PRT
 <213> Homo sapiens

<400> 638
 Phe Ser Arg Asp Lys Val Ser Pro Cys Trp Pro Gly Trp Ser Arg Thr
 1 5 10 15

Pro Gly Leu Arg
 20

<210> 639
 <211> 408
 <212> PRT
 <213> Homo sapiens

<400> 639
 Thr Trp Gly Gln Thr Pro Cys Ser Pro Gly His Gly Gln Arg Pro Ser
 1 5 10 15

Ser Thr Cys Leu Thr Val Gly Pro Gly Gly Gly Pro Ser Leu Gly Arg
 20 25 30

Pro Cys Pro Gln Leu Leu Leu Gln Phe Gly Val Leu Phe Cys Thr Ile
 35 40 45

597

Leu Leu Leu Leu Trp Val Ser Val Phe Leu Tyr Gly Ser Phe Tyr Tyr
 50 55 60

Ser Tyr Met Pro Thr Val Ser His Leu Ser Pro Val His Phe Tyr Tyr
 65 70 75 80

Arg Thr Asp Cys Asp Ser Ser Thr Thr Ser Leu Cys Ser Phe Pro Val
 85 90 95

Ala Asn Val Ser Leu Thr Lys Gly Gly Arg Asp Arg Val Leu Met Tyr
 100 105 110

Gly Gln Pro Tyr Arg Val Thr Leu Glu Leu Glu Leu Pro Glu Ser Pro
 115 120 125

Val Asn Gln Asp Leu Gly Met Phe Leu Val Thr Ile Ser Cys Tyr Thr
 130 135 140

Arg Gly Gly Arg Ile Ile Ser Thr Ser Ser Arg Ser Val Met Leu His
 145 150 155 160

Tyr Arg Ser Asp Leu Leu Gln Met Leu Asp Thr Leu Val Phe Ser Ser
 165 170 175

Leu Leu Leu Phe Gly Phe Ala Glu Gln Lys Gln Leu Leu Glu Val Glu
 180 185 190

Leu Tyr Ala Asp Tyr Arg Glu Asn Ser Tyr Val Pro Thr Thr Gly Ala
 195 200 205

Ile Ile Glu Ile His Ser Lys Arg Ile Gln Leu Tyr Gly Ala Tyr Leu
 210 215 220

Arg Ile His Ala His Phe Thr Gly Leu Arg Tyr Leu Leu Tyr Asn Phe
 225 230 235 240

Pro Met Thr Cys Ala Phe Ile Gly Val Ala Ser Asn Phe Thr Phe Leu
 245 250 255

Ser Val Ile Val Leu Phe Ser Tyr Met Gln Trp Val Trp Gly Gly Ile
 260 265 270

Trp Pro Arg His Arg Phe Ser Leu Gln Val Asn Ile Arg Lys Arg Asp
 275 280 285

Asn Ser Arg Lys Glu Val Gln Arg Arg Ile Ser Ala His Gln Pro Gly
 290 295 300

Pro Glu Gly Gln Glu Glu Ser Thr Pro Gln Ser Asp Val Thr Glu Asp
 305 310 315 320

Gly Glu Ser Pro Glu Asp Pro Ser Gly Thr Glu Gly Gln Leu Ser Glu
325 330 335

Glu Glu Lys Pro Asp Gln Gln Pro Leu Ser Gly Glu Glu Gln Leu Glu
340 345 350

Pro Glu Ala Ser Asp Gly Ser Gly Ser Trp Glu Asp Ala Ala Leu Leu
355 360 365

Thr Glu Ala Asn Leu Pro Ala Pro Ala Pro Ala Ser Ala Ser Ala Pro
370 375 380

Val Leu Glu Thr Leu Gly Ser Ser Glu Pro Ala Gly Gly Ala Leu Arg
385 390 395 400

Gln Arg Pro Thr Cys Ser Ser Ser
405

<210> 640

<211> 288

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (268)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (271)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (273)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE
 <222> (274)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (276)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (286)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 640

Phe Ser Ser Ser Ala Cys Pro Ser Val Xaa Ser Leu Phe Val Xaa Leu
 1 5 10 15

Gly Lys Asn Pro His Asp Ala Gln Gly His Pro Arg Ala Ser Glu Asp
 20 25 30

Gln Pro Ser Ser Gly Lys Pro Val Thr Ser Tyr Pro Gly Glu Cys Gly
 35 40 45

Phe Val Phe Thr Lys Glu Ala Ser Leu Glu Ile Arg Asp Met Leu Leu
 50 55 60

Ala Asn Lys Val Pro Ala Ala Ala Arg Ala Gly Ala Ile Ala Pro Cys
 65 70 75 80

Glu Val Thr Val Pro Ala Gln Asn Thr Gly Leu Gly Pro Glu Lys Thr
 85 90 95

Ser Phe Phe Gln Ala Leu Gly Ile Thr Thr Lys Ile Ser Arg Gly Thr
 100 105 110

Ile Glu Ile Leu Ser Asp Val Gln Leu Ile Lys Thr Gly Asp Lys Val
 115 120 125

Gly Ala Ser Glu Ala Thr Leu Leu Asn Met Leu Asn Ile Ser Pro Phe
 130 135 140

Ser Phe Gly Leu Ile Ile Gln Gln Val Phe Asp Asn Gly Ser Ile Tyr
 145 150 155 160

Asn Pro Glu Val Leu Asp Ile Thr Glu Glu Thr Leu His Ser Arg Phe
 165 170 175

Leu Glu Gly Val Arg Asn Val Ala Ser Val Cys Leu Gln Ile Gly Tyr
 180 185 190

600

Pro Thr Val Ala Ser Val Pro His Ser Ile Ile Asn Gly Tyr Lys Arg
 195 200 205

Val Leu Ala Leu Ser Val Glu Thr Asp Tyr Thr Phe Pro Leu Ala Glu
 210 215 220

Lys Val Lys Ala Phe Leu Ala Asp Pro Ser Ala Phe Val Ala Ala Ala
 225 230 235 240

Pro Val Ala Ala Ala Thr Thr Ala Ala Pro Ala Ala Ala Ala Pro
 245 250 255

Ala Lys Val Glu Ala Lys Glu Glu Ser Glu Glu Xaa Asp Glu Xaa Ile
 260 265 270

Xaa Xaa Ser Xaa Ile Ser Lys Ser Asn Asn Ser Ser Gln Xaa Ile Val
 275 280 285

<210> 641

<211> 444

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (34)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 641

Asn Glu Gln Asp Asn Cys Val Leu Ile His Asp Val Asp Gln Arg Asn
 1 5 10 15

Ser Asp Lys Asp Ile Phe Gly Asp Ala Cys Asp Asn Cys Leu Ser Val
 20 25 30

Leu Xaa Asn Asp Gln Lys Asp Thr Asp Gly Asp Gly Arg Gly Asp Ala
 35 40 45

Cys Asp Asp Asp Met Asp Gly Ile Lys Asn Ile Leu Asp Asn
 50 55 60

Cys Pro Lys Phe Pro Asn Arg Asp Gln Arg Asp Lys Asp Gly Asp Gly
 65 70 75 80

Val Gly Asp Ala Cys Asp Ser Cys Pro Asp Val Ser Asn Pro Asn Gln
 85 90 95

Ser Asp Val Asp Asn Asp Leu Val Gly Asp Ser Cys Asp Thr Asn Gln
100 105 110

Asp Ser Asp Gly Asp Gly His Gln Asp Ser Thr Asp Asn Cys Pro Thr
115 120 125

Val Ile Asn Ser Ala Gln Leu Asp Thr Asp Lys Asp Gly Ile Gly Asp
130 135 140

Glu Cys Asp Asp Asp Asp Asn Asp Gly Ile Pro Asp Leu Val Pro
145 150 155 160

Pro Gly Pro Asp Asn Cys Arg Leu Val Pro Asn Pro Ala Gln Glu Asp
165 170 175

Ser Asn Ser Asp Gly Val Gly Asp Ile Cys Glu Ser Asp Phe Asp Gln
180 185 190

Asp Gln Val Ile Asp Arg Ile Asp Val Cys Pro Glu Asn Ala Glu Val
195 200 205

Thr Leu Thr Asp Phe Arg Ala Tyr Gln Thr Val Val Leu Asp Pro Glu
210 215 220

Gly Asp Ala Gln Ile Asp Pro Asn Trp Val Val Leu Asn Gln Gly Met
225 230 235 240

Glu Ile Val Gln Thr Met Asn Ser Asp Pro Gly Leu Ala Val Gly Tyr
245 250 255

Thr Ala Phe Asn Gly Val Asp Phe Glu Gly Thr Phe His Val Asn Thr
260 265 270

Gln Thr Asp Asp Asp Tyr Ala Gly Phe Ile Phe Gly Tyr Gln Asp Ser
275 280 285

Ser Ser Phe Tyr Val Val Met Trp Lys Gln Thr Glu Gln Thr Tyr Trp
290 295 300

Gln Ala Thr Pro Phe Arg Ala Val Ala Glu Pro Gly Ile Gln Leu Lys
305 310 315 320

Ala Val Lys Ser Lys Thr Gly Pro Gly Glu His Leu Arg Asn Ser Leu
325 330 335

Trp His Thr Gly Asp Thr Ser Asp Gln Val Arg Leu Leu Trp Lys Asp
340 345 350

Ser Arg Asn Val Gly Trp Lys Asp Lys Val Ser Tyr Arg Trp Phe Leu
355 360 365

602

Gln His Arg Pro Gln Val Gly Tyr Ile Arg Val Arg Phe Tyr Glu Gly
 370 375 380

Ser Glu Leu Val Ala Asp Ser Gly Val Thr Ile Asp Thr Thr Met Arg
 385 390 395 400

Gly Gly Arg Leu Gly Val Phe Cys Phe Ser Gln Glu Asn Ile Ile Trp
 405 410 415

Ser Asn Leu Lys Tyr Arg Cys Asn Asp Thr Ile Pro Glu Asp Phe Gln
 420 425 430

Glu Phe Gln Thr Gln Asn Phe Asp Arg Phe Asp Asn
 435 440

<210> 642

<211> 326

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (296)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 642

Ser Ala Arg Ala Ser Asp Leu Gly Ala Pro Arg Thr Trp Thr Gly Ala
 1 5 10 15

Ala Ala Gly Pro Arg Thr Pro Ser Ala His Ile Pro Val Pro Ala Gln
 20 25 30

Arg Ala Thr Pro Gly Lys Ala Arg Leu Asp Glu Val Met Ala Ala Ala
 35 40 45

Ala Xaa Thr Ser Leu Ser Thr Ser Pro Leu Leu Leu Gly Ala Pro Val
 50 55 60

Ala Ala Phe Ser Pro Glu Pro Gly Leu Glu Pro Trp Lys Glu Ala Leu
 65 70 75 80

Val Arg Pro Pro Gly Ser Tyr Ser Ser Ser Ser Asn Ser Gly Asp Trp
 85 90 95

603

Gly Trp Asp Leu Ala Ser Asp Gln Ser Ser Pro Ser Thr Pro Ser Pro
 100 105 110
 Pro Leu Pro Pro Glu Ala Ala His Phe Leu Phe Gly Glu Pro Thr Leu
 115 120 125
 Arg Lys Arg Lys Ser Pro Ala Gln Val Met Phe Gln Cys Leu Trp Lys
 130 135 140
 Ser Cys Gly Lys Val Leu Ser Thr Ala Ser Ala Met Gln Arg His Ile
 145 150 155 160
 Arg Leu Val His Leu Gly Arg Gln Ala Glu Pro Asp Gln Ser Asp Gly
 165 170 175
 Glu Glu Asp Phe Tyr Tyr Thr Glu Leu Asp Val Gly Val Asp Thr Leu
 180 185 190
 Thr Asp Gly Leu Ser Ser Leu Thr Pro Val Ser Pro Thr Ala Ser Met
 195 200 205
 Pro Pro Ala Phe Pro Arg Leu Glu Leu Pro Glu Leu Leu Glu Pro Pro
 210 215 220
 Ala Leu Pro Ser Pro Leu Arg Pro Pro Ala Pro Pro Leu Pro Pro Pro
 225 230 235 240
 Pro Val Leu Ser Thr Val Ala Asn Pro Gln Ser Cys His Ser Asp Arg
 245 250 255
 Val Tyr Gln Gly Cys Leu Thr Pro Ala Arg Leu Glu Pro Gln Pro Thr
 260 265 270
 Glu Val Gly Ala Cys Pro Pro Ala Leu Ser Ser Arg Ile Gly Val Thr
 275 280 285
 Leu Arg Lys Pro Arg Gly Asp Xaa Lys Lys Cys Arg Lys Val Tyr Gly
 290 295 300
 Met Glu Arg Arg Asp Leu Trp Cys Thr Ala Cys Arg Trp Lys Lys Ala
 305 310 315 320
 Cys Gln Arg Phe Leu Asp
 325

<210> 643

<211> 129

<212> PRT

604

<213> Homo sapiens

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (14)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (18)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (19)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (24)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (94)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (103)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 643

Asp Val Arg Leu Ser Gly Arg Asn Xaa Xaa Val Asp Val Xaa Asp His

1

5

10

15

605

Gln Xaa Xaa Leu Leu Glu Gln Xaa Asp Leu Leu Ala Gly Leu Ile Ser
 20 25 30

Asn Ser Ser Asp Ala Xaa Asp Lys Ile Arg Tyr Glu Ser Leu Thr Asp
 35 40 45

Pro Ser Lys Leu Asp Ser Gly Lys Glu Leu His Ile Asn Leu Ile Pro
 50 55 60

Asn Lys Gln Asp Arg Thr Leu Thr Ile Val Gly Tyr Arg Asp Arg Met
 65 70 75 80

Thr Lys Ala Asp Leu Ile Asn Asn Leu Gly Thr Ile Ala Xaa Ser Gly
 85 90 95

Thr Lys Ala Phe Met Glu Xaa Leu Gln Ala Gly Ala Asp Ile Ser Met
 100 105 110

Ile Gly Gln Phe Gly Val Gly Phe Tyr Ser Ala Tyr Leu Val Ala Arg
 115 120 125

Arg

<210> 644

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (12)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 644

Ser Thr His Ala Ser Ala Ser Arg Arg Leu Leu Xaa Asp Val Cys Gln
 1 5 10 15

Asp Cys Ile Gln Met Val Thr Asp Ile Gln Thr Ala Val Arg Thr Asn
 20 25 30

Ser Thr Phe Val Glu Ala Leu Val Asp His Ala Lys Ala Gln Cys Asp
 35 40 45

Leu Leu Gly Pro Gly Met Ala Asp Met Cys Lys Asn Tyr Ile Asn Gln
 50 55 60

Tyr Ser Asp Ile Ala Val Gln Met Met Met His Met Gln Pro Lys Glu
 65 70 75 80

606

Ile Cys Gly Leu Val Gly Phe Cys Asp Gln Val Lys Glu Met Pro Met
 85 90 95

Gln Thr Leu Ile Pro Ala Lys Ala Val Ser Glu Asn Val Ile Pro Ala
 100 105 110

Leu Glu Leu Val Glu Pro Ile Lys Lys Asp Thr Val Gln Ala Lys Thr
 115 120 125

Ser Val Ser Cys Gly Asp Met Arg Val Thr Trp Leu Lys Glu Val Ala
 130 135 140

Lys Leu His Trp Thr Thr Thr Gly Leu Arg Lys Lys
 145 150 155

<210> 645

<211> 115

<212> PRT

<213> Homo sapiens

<400> 645

Ala Asp Pro Gly Val Gly Ala Val Pro Gly Leu Ala Ala Asp Leu Ala
 1 5 10 15

Thr Ala Ala Arg Ser Leu Gly Pro Ala Leu Val Leu Asp Leu Gly Arg
 20 25 30

Pro Pro Ser Pro Asp Pro His Glu Gly Pro Ser Pro Ser Pro Arg Arg
 35 40 45

Ser Pro Asp Leu Val Arg Gly Pro Gly Pro Gly Leu Gly Pro Gly Val
 50 55 60

Leu Pro Gln Cys Pro Arg Gly Asn Pro Asn Pro Gly Arg Asp Arg Arg
 65 70 75 80

Val Pro Pro Ser Leu Leu Lys Arg Lys Glu Arg Cys Pro Leu Lys Lys
 85 90 95

Met Val Met Ser Gly Asn Pro Arg His Ile Thr Leu Ile His Lys Trp
 100 105 110

Asp Leu Gly
 115

<210> 646

607

<211> 153
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (127)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 646

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| Tyr | Met | Pro | Asn | Gly | Ser | Leu | Asn | Glu | Leu | Leu | His | Arg | Lys | Thr | Glu | 1 | 5 | 10 | 15 |
| Tyr | Pro | Asp | Val | Ala | Trp | Pro | Leu | Arg | Phe | Arg | Ile | Leu | His | Glu | Ile | 20 | 25 | 30 | |
| Ala | Leu | Gly | Val | Asn | Tyr | Leu | His | Asn | Met | Thr | Pro | Pro | Leu | Leu | His | 35 | 40 | 45 | |
| His | Asp | Leu | Lys | Thr | Gln | Asn | Ile | Leu | Leu | Asp | Asn | Glu | Phe | His | Val | 50 | 55 | 60 | |
| Lys | Ile | Ala | Asp | Phe | Gly | Leu | Ser | Lys | Trp | Arg | Met | Met | Ser | Leu | Ser | 65 | 70 | 75 | 80 |
| Gln | Ser | Arg | Ser | Ser | Lys | Ser | Ala | Pro | Glu | Gly | Gly | Thr | Ile | Ile | Tyr | 85 | 90 | 95 | |
| Met | Pro | Pro | Glu | Asn | Tyr | Glu | Pro | Gly | Gln | Lys | Ser | Arg | Ala | Ser | Ile | 100 | 105 | 110 | |
| Lys | His | Asp | Ile | Tyr | Ser | Tyr | Ala | Val | Ile | Thr | Trp | Glu | Val | Xaa | Ser | 115 | 120 | 125 | |
| Arg | Lys | Gln | Pro | Phe | Glu | Asp | Val | Thr | Asn | Pro | Leu | Gln | Ile | Met | Tyr | 130 | 135 | 140 | |
| Ser | Val | Ser | Gln | Gly | His | Trp | Thr | Gly | | | | | | | | 145 | 150 | | |

<210> 647
 <211> 220
 <212> PRT
 <213> Homo sapiens

<400> 647

| | | | | | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|---|----|----|
| Ala | Ser | Glu | Gln | Gly | Ala | Val | Gly | Gln | Gly | Gly | Leu | Ala | Gly | Val | Pro | 1 | 5 | 10 | 15 |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|---|---|----|----|

608

Thr Leu Thr Ser Leu Pro Ser Ser Cys Pro Glu Pro Arg Pro Ser Met
 20 25 30
 Asp Ala Val Asp Ala Thr Met Glu Lys Leu Arg Ala Gln Cys Leu Ser
 35 40 45
 Arg Gly Ala Ser Gly Ile Gln Gly Leu Ala Arg Phe Phe Arg Gln Leu
 50 55 60
 Asp Arg Asp Gly Ser Arg Ser Leu Asp Ala Asp Glu Phe Arg Gln Gly
 65 70 75 80
 Leu Ala Lys Leu Gly Leu Val Leu Asp Gln Ala Glu Ala Glu Gly Val
 85 90 95
 Cys Arg Lys Trp Asp Arg Asn Gly Ser Gly Thr Leu Asp Leu Glu Glu
 100 105 110
 Phe Leu Arg Ala Leu Arg Pro Pro Met Ser Gln Ala Arg Glu Ala Val
 115 120 125
 Ile Ala Ala Ala Phe Ala Lys Leu Asp Arg Ser Gly Asp Gly Val Val
 130 135 140
 Thr Val Asp Asp Leu Arg Gly Val Tyr Ser Gly Arg Ala His Pro Lys
 145 150 155 160
 Val Arg Ser Gly Glu Trp Thr Glu Asp Glu Val Leu Arg Arg Phe Leu
 165 170 175
 Asp Asn Phe Asp Ser Ser Glu Lys Asp Gly Gln Val Thr Leu Ala Glu
 180 185 190
 Phe Gln Asp Tyr Tyr Ser Gly Val Ser Ala Ser Met Asn Thr Asp Glu
 195 200 205
 Glu Phe Val Ala Met Met Thr Ser Ala Trp Gln Leu
 210 215 220

<210> 648

<211> 118

<212> PRT

<213> Homo sapiens

<400> 648

Asp Asn Arg Thr Leu Thr Lys Gly Pro Asp Thr Val Gly Thr Met Gly
 1 5 10 15

Gln Cys Arg Ser Ala Asn Ala Glu Asp Ala Gln Glu Phe Ser Asp Val

609

20 25 30
 Glu Arg Ala Ile Glu Thr Leu Ile Lys Asn Phe His Gln Tyr Ser Val
 35 40 45
 Glu Gly Gly Lys Glu Thr Leu Thr Pro Ser Glu Leu Arg Asp Leu Val
 50 55 60
 Thr Gln Gln Leu Pro His Leu Met Pro Ser Asn Cys Gly Leu Glu Glu
 65 70 75 80
 Lys Ile Ala Asn Leu Gly Ser Cys Asn Asp Ser Lys Leu Glu Phe Arg
 85 90 95
 Ser Phe Trp Glu Leu Ile Gly Glu Ala Ala Lys Ser Val Lys Leu Glu
 100 105 110
 Arg Pro Val Arg Gly His
 115

<210> 649

<211> 309

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (77)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (160)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 649

Asp His His Gln Gly Ala Glu Ser Val Pro Gly Ile Gly Val Ser Pro
 1 5 10 15

Thr Ser Ser Ser Ser Cys Pro Pro Thr Ser Cys Thr Gln Pro Val Thr
 20 25 30

Thr Trp Ser Pro Gly Leu Arg Val Glu Ser Leu Asp Gly Ala Lys Thr
 35 40 45

Gly Lys Gly Ala Leu Thr Gly Ala Pro Gly Ser Phe Gly Ser Ser Glu
 50 55 60

Phe Leu Thr Gly Leu Arg Asn Thr Ser Glu Ala Arg Xaa Thr Arg Gly

610

65 70 75 80
 Pro Ile Met Gln Glu Pro Arg Arg Val Thr Pro Cys Leu Gly Lys Arg
 85 90 95
 Gly Val Lys Thr Pro Gln Leu Gln Pro Gly Ser Ala Phe Leu Pro Arg
 100 105 110
 Val Arg Arg Gln Ser Phe Pro Ala Arg Ser Asp Ser Tyr Thr Thr Val
 115 120 125
 Arg Asp Phe Leu Ala Val Pro Arg Thr Ile Ser Ser Ala Ser Ala Thr
 130 135 140
 Leu Ile Met Ala Val Ala Val Ser His Phe Arg Pro Gly Pro Glu Xaa
 145 150 155 160
 Trp Asp Thr Ala Ser Met Ala Ala Ser Lys Val Lys Gln Asp Met Pro
 165 170 175
 Pro Pro Gly Gly Tyr Gly Pro Ile Asp Tyr Lys Arg Asn Leu Pro Arg
 180 185 190
 Arg Gly Leu Ser Gly Tyr Ser Met Leu Ala Ile Gly Ile Gly Thr Leu
 195 200 205
 Ile Tyr Gly His Trp Ser Ile Met Lys Trp Asn Arg Glu Arg Arg Arg
 210 215 220
 Leu Gln Ile Glu Asp Phe Glu Ala Arg Ile Ala Leu Leu Pro Leu Leu
 225 230 235 240
 Gln Ala Glu Thr Asp Arg Arg Thr Leu Gln Met Leu Arg Glu Asn Leu
 245 250 255
 Glu Glu Glu Ala Ile Ile Met Lys Asp Val Pro Asp Trp Lys Val Gly
 260 265 270
 Glu Ser Val Phe His Thr Thr Arg Trp Val Pro Pro Leu Ile Gly Glu
 275 280 285
 Leu Tyr Gly Leu Arg Thr Thr Glu Glu Ala Leu His Ala Ser His Gly
 290 295 300
 Phe Met Trp Tyr Thr
 305

<210> 650

<211> 286

611

<212> PRT

<213> Homo sapiens

<400> 650

Ile Pro Thr Leu Ile Thr Ala Phe Val Leu Ala Thr Ser Gln Ala Gln
1 5 10 15
Ala Gly Trp Leu Gln His Asp Tyr Gly His Leu Ser Val Tyr Arg Lys
20 25 30
Pro Lys Trp Asn His Leu Val His Lys Phe Val Ile Gly His Leu Lys
35 40 45
Gly Ala Ser Ala Asn Trp Trp Asn His Arg His Phe Gln His His Ala
50 55 60
Lys Pro Asn Ile Phe His Lys Asp Pro Asp Val Asn Met Leu His Val
65 70 75 80
Phe Val Leu Gly Glu Trp Gln Pro Ile Glu Tyr Gly Lys Lys Lys Leu
85 90 95
Lys Tyr Leu Pro Tyr Asn His Gln His Glu Tyr Phe Phe Leu Ile Gly
100 105 110
Pro Pro Leu Leu Ile Pro Met Tyr Phe Gln Tyr Gln Ile Ile Met Thr
115 120 125
Met Ile Val His Lys Asn Trp Val Asp Leu Ala Trp Ala Val Ser Tyr
130 135 140
Tyr Ile Arg Phe Phe Ile Thr Tyr Ile Pro Phe Tyr Gly Ile Leu Gly
145 150 155 160
Ala Leu Leu Phe Leu Asn Phe Ile Arg Phe Leu Glu Ser His Trp Phe
165 170 175
Val Trp Val Thr Gln Met Asn His Ile Val Met Glu Ile Asp Gln Glu
180 185 190
Ala Tyr Arg Asp Trp Phe Ser Ser Gln Leu Thr Ala Thr Cys Asn Val
195 200 205
Glu Gln Ser Phe Phe Asn Asp Trp Phe Ser Gly His Leu Asn Phe Gln
210 215 220
Ile Glu His His Leu Phe Pro Thr Met Pro Arg His Asn Leu His Lys
225 230 235 240
Ile Ala Pro Leu Val Lys Ser Leu Cys Ala Lys His Gly Ile Glu Tyr
245 250 255

Gln Glu Lys Pro Leu Leu Arg Ala Leu Leu Asp Ile Ile Arg Ser Leu
 260 265 270

Lys Lys Ser Gly Lys Leu Trp Leu Asp Ala Tyr Leu His Lys
 275 280 285

<210> 651

<211> 184

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (35)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (57)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (71)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (106)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 651

Glu Arg Gly Pro Ile Pro Val Cys Pro His Lys Ala Ala Ser Ser Val
 1 5 10 15

Ile Ser Leu Leu Arg Ala Glu Leu Arg Leu Tyr Thr Asp Pro His Lys
 20 25 30

Tyr His Xaa Phe Cys Leu Arg Lys Asp Lys Ala His Val Cys Phe Cys
 35 40 45

Phe Arg Phe Leu Phe Ser Phe Phe Xaa Glu Ala Leu Trp Arg Ser Met
 50 55 60

Phe Leu Leu Ser Phe Leu Xaa Lys Pro Ser Phe Trp Ala Thr Gly Leu
 65 70 75 80

Ile Leu Ser Thr Ser Ser Phe Pro Pro Phe Ser Ile Val Ser Leu Pro

613

| | | |
|---|-----------------|-------------------------------------|
| 85 | 90 | 95 |
| Pro Ser His | Pro Thr Arg Ala | Pro Leu Xaa Leu Ser Phe Pro Ser Ser |
| 100 | 105 | 110 |
| Pro Ala Val Ser Phe Leu Arg Ser Gly Thr Lys Leu Ile Phe Arg Arg | | |
| 115 | 120 | 125 |
| Arg Pro Arg Gln Lys Glu Ala Gly Leu Ser Gln Ser His Asp Asp Leu | | |
| 130 | 135 | 140 |
| Ser Asn Ala Thr Ala Thr Pro Ser Val Arg Lys Lys Ala Gly Ser Phe | | |
| 145 | 150 | 155 |
| Ser Arg Arg Leu Ile Lys Arg Phe Ser Phe Lys Ser Lys Pro Lys Ala | | |
| 165 | 170 | 175 |
| Asn Gly Asn Pro Ser Pro Gln Leu | | |
| 180 | | |

<210> 652

<211> 641

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (438)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 652

| | | |
|---|----|----|
| Gln Gly Ser Glu Pro Ser Ser Glu Asn Ala Asn Asp Thr Ile Ile Leu | | |
| 1 | 5 | 10 |
| Arg Asn Leu Asn Pro His Ser Thr Met Asp Ser Ile Leu Gly Ala Leu | | |
| 20 | 25 | 30 |
| Ala Pro Tyr Ala Val Leu Ser Ser Ser Asn Val Arg Val Ile Lys Asp | | |
| 35 | 40 | 45 |
| Lys Gln Thr Gln Leu Asn Arg Gly Phe Ala Phe Ile Gln Leu Ser Thr | | |
| 50 | 55 | 60 |
| Ile Glu Ala Ala Gln Leu Leu Gln Ile Leu Gln Ala Leu His Pro Pro | | |
| 65 | 70 | 75 |
| Leu Thr Ile Asp Gly Lys Thr Ile Asn Val Glu Phe Ala Lys Gly Ser | | |
| 85 | 90 | 95 |

Lys Arg Asp Met Ala Ser Asn Glu Gly Ser Arg Ile Ser Ala Ala Ser
 100 105 110
 Val Ala Ser Thr Ala Ile Ala Ala Ala Gln Trp Ala Ile Ser Gln Ala
 115 120 125
 Ser Gln Gly Gly Glu Gly Thr Trp Ala Thr Ser Glu Glu Pro Pro Val
 130 135 140
 Asp Tyr Ser Tyr Tyr Gln Gln Asp Glu Gly Tyr Gly Asn Ser Gln Gly
 145 150 155 160
 Thr Glu Ser Ser Leu Tyr Ala His Gly Tyr Leu Lys Gly Thr Lys Gly
 165 170 175
 Pro Gly Ile Thr Gly Thr Lys Gly Asp Pro Thr Gly Ala Gly Pro Glu
 180 185 190
 Ala Ser Leu Glu Pro Gly Ala Asp Ser Val Ser Met Gln Ala Phe Ser
 195 200 205
 Arg Ala Gln Pro Gly Ala Ala Pro Gly Ile Tyr Gln Gln Ser Ala Glu
 210 215 220
 Ala Ser Ser Ser Gln Gly Thr Ala Ala Asn Ser Gln Ser Tyr Thr Ile
 225 230 235 240
 Met Ser Pro Ala Val Leu Lys Ser Glu Leu Gln Ser Pro Thr His Pro
 245 250 255
 Ser Ser Ala Leu Pro Pro Ala Thr Ser Pro Thr Ala Gln Glu Ser Tyr
 260 265 270
 Ser Gln Tyr Pro Val Pro Asp Val Ser Thr Tyr Gln Tyr Asp Glu Thr
 275 280 285
 Ser Gly Tyr Tyr Tyr Asp Pro Gln Thr Gly Leu Tyr Tyr Asp Pro Asn
 290 295 300
 Ser Gln Tyr Tyr Tyr Asn Ala Gln Ser Gln Gln Tyr Leu Tyr Trp Asp
 305 310 315 320
 Gly Glu Arg Arg Thr Tyr Val Pro Ala Leu Glu Gln Ser Ala Asp Gly
 325 330 335
 His Lys Glu Thr Gly Ala Pro Ser Lys Glu Gly Lys Glu Lys Lys Glu
 340 345 350
 Lys His Lys Thr Lys Thr Ala Gln Gln Ile Ala Lys Asp Met Glu Arg
 355 360 365

615

Trp Ala Arg Ser Leu Asn Lys Gln Lys Glu Asn Phe Lys Asn Ser Phe
370 375 380

Gln Pro Ile Ser Ser Leu Arg Asp Asp Glu Arg Arg Glu Ser Ala Thr
385 390 395 400

Ala Asp Ala Gly Tyr Ala Ile Leu Glu Lys Lys Gly Ala Leu Ala Glu
405 410 415

Arg Gln His Thr Ser Met Asp Leu Pro Lys Leu Ala Ser Asp Asp Arg
420 425 430

Pro Ser Pro Pro Arg Xaa Leu Val Ala Ala Tyr Ser Gly Glu Ser Asp
435 440 445

Ser Glu Glu Glu Gln Glu Arg Gly Gly Pro Glu Arg Glu Glu Lys Leu
450 455 460

Thr Asp Trp Gln Lys Leu Ala Cys Leu Leu Cys Arg Arg Gln Phe Pro
465 470 475 480

Ser Lys Glu Ala Leu Ile Arg His Gln Gln Leu Ser Gly Leu His Lys
485 490 495

Gln Asn Leu Glu Ile His Arg Arg Ala His Leu Ser Glu Asn Glu Leu
500 505 510

Glu Ala Leu Glu Lys Asn Asp Met Glu Gln Met Lys Tyr Arg Asp Arg
515 520 525

Ala Ala Glu Arg Arg Glu Lys Tyr Gly Ile Pro Glu Pro Pro Glu Pro
530 535 540

Lys Arg Arg Lys Tyr Gly Gly Ile Ser Thr Ala Ser Val Asp Phe Glu
545 550 555 560

Gln Pro Thr Arg Asp Gly Leu Gly Ser Asp Asn Ile Gly Ser Arg Met
565 570 575

Leu Gln Ala Met Gly Trp Lys Glu Gly Ser Gly Leu Gly Arg Lys Lys
580 585 590

Gln Gly Ile Val Thr Pro Ile Glu Ala Gln Thr Arg Val Arg Gly Ser
595 600 605

Gly Leu Gly Ala Arg Gly Ser Ser Tyr Gly Val Thr Ser Thr Glu Ser
610 615 620

Tyr Lys Glu Thr Leu His Lys Thr Met Val Thr Arg Phe Asn Glu Ala
625 630 635 640

616

Gln

<210> 653

<211> 516

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (247)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 653

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Thr | Arg | Pro | Gly | Arg | Gln | Thr | Arg | Leu | Cys | Arg | Pro | Ala | Ile | Ser |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Leu | Trp | Leu | Val | Thr | Pro | Gly | Val | Pro | Ala | Phe | Ser | Gly | Trp | Gly |
| | | | 20 | | | | | 25 | | | | | | 30 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Arg | His | Arg | Gly | Arg | Thr | Gly | Arg | Arg | Ala | Met | Ala | Ser | Cys | Val |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ser | Arg | Thr | Leu | Ser | Lys | Asp | Asp | Val | Asn | Tyr | Lys | Met | His | Phe |
| | 50 | | | | | 55 | | | | | | | 60 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Met | Ile | Asn | Glu | Gln | Gln | Val | Glu | Asp | Ile | Thr | Ile | Asp | Phe | Phe |
| 65 | | | | 70 | | | | | 75 | | | | | 80 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Arg | Pro | His | Thr | Ile | Thr | Leu | Leu | Ser | Phe | Thr | Ile | Val | Ser | Leu |
| | | | 85 | | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Met | Tyr | Phe | Ala | Phe | Thr | Arg | Asp | Asp | Ser | Val | Pro | Glu | Asp | Asn | Ile |
| | | 100 | | | | | | 105 | | | | | | 110 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Arg | Gly | Ile | Leu | Ser | Val | Ile | Phe | Phe | Phe | Leu | Ile | Ile | Ser | Val |
| | | 115 | | | | | 120 | | | | | 125 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ala | Phe | Pro | Asn | Gly | Pro | Phe | Thr | Arg | Pro | His | Pro | Ala | Leu | Trp |
| | 130 | | | | | | 135 | | | | | 140 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Arg | Met | Val | Phe | Gly | Leu | Ser | Val | Leu | Tyr | Phe | Leu | Phe | Leu | Val | Phe |
| 145 | | | | | 150 | | | | | 155 | | | | | 160 |

Leu Leu Phe Leu Asn Phe Glu Gln Val Lys Ser Leu Met Tyr Trp Leu
 165 170 175
 Asp Pro Asn Leu Arg Tyr Ala Thr Arg Glu Ala Asp Val Met Glu Tyr
 180 185 190
 Ala Val Asn Cys His Val Ile Thr Trp Glu Arg Ile Ile Ser His Phe
 195 200 205
 Asp Ile Phe Ala Phe Gly His Phe Trp Gly Trp Ala Met Lys Ala Leu
 210 215 220
 Leu Ile Arg Ser Tyr Gly Leu Cys Trp Thr Ile Ser Ile Thr Trp Glu
 225 230 235 240
 Leu Thr Glu Leu Phe Phe Xaa His Leu Leu Pro Asn Phe Ala Glu Cys
 245 250 255
 Trp Trp Asp Gln Val Ile Leu Asp Ile Leu Leu Cys Asn Gly Gly Gly
 260 265 270
 Ile Trp Leu Gly Met Val Val Cys Arg Phe Leu Glu Met Arg Thr Tyr
 275 280 285
 His Trp Ala Ser Phe Lys Asp Ile His Thr Thr Thr Gly Lys Ile Lys
 290 295 300
 Arg Ala Val Leu Gln Phe Thr Pro Ala Ser Trp Thr Tyr Val Arg Trp
 305 310 315 320
 Phe Asp Pro Lys Ser Ser Phe Gln Arg Val Ala Gly Val Tyr Leu Phe
 325 330 335
 Met Ile Ile Trp Gln Leu Thr Glu Leu Asn Thr Phe Phe Leu Lys His
 340 345 350
 Ile Phe Val Phe Gln Ala Ser His Pro Leu Ser Trp Gly Arg Ile Leu
 355 360 365
 Phe Ile Gly Gly Ile Thr Ala Pro Thr Val Arg Gln Tyr Tyr Ala Tyr
 370 375 380
 Leu Thr Asp Thr Gln Cys Lys Arg Val Gly Thr Gln Cys Trp Val Phe
 385 390 395 400
 Gly Val Ile Gly Phe Leu Glu Ala Ile Val Cys Ile Lys Phe Gly Gln
 405 410 415
 Asp Leu Phe Ser Lys Thr Gln Ile Leu Tyr Val Val Leu Trp Leu Leu
 420 425 430

618

Cys Val Ala Phe Thr Thr Phe Leu Cys Leu Tyr Gly Met Ile Trp Tyr
 435 440 445

Ala Glu His Tyr Gly His Arg Glu Lys Thr Tyr Ser Glu Cys Glu Asp
 450 455 460

Gly Thr Tyr Ser Pro Glu Ile Ser Trp His His Arg Lys Gly Thr Lys
 465 470 475 480

Gly Ser Glu Asp Ser Pro Pro Lys His Ala Gly Asn Asn Glu Ser His
 485 490 495

Ser Ser Arg Arg Arg Asn Arg His Ser Lys Ser Lys Val Thr Asn Gly
 500 505 510

Val Gly Lys Lys
 515

<210> 654

<211> 663

<212> PRT

<213> Homo sapiens

<400> 654

Leu Glu Cys Arg Glu Ala His Ile Arg Asp Val Pro Val Val Arg Leu
 1 5 10 15

Pro Ala Asp Ser Pro Ile Pro Glu Arg Gly Asp Leu Ser Cys Arg Met
 20 25 30

His Thr Cys Phe Asp Val Tyr Arg Cys Gly Phe Asn Pro Lys Asn Lys
 35 40 45

Ile Lys Val Tyr Ile Tyr Ala Leu Lys Lys Tyr Val Asp Asp Phe Gly
 50 55 60

Val Ser Val Ser Asn Thr Ile Ser Arg Glu Tyr Asn Glu Leu Leu Met
 65 70 75 80

Ala Ile Ser Asp Ser Asp Tyr Tyr Thr Asp Asp Ile Asn Arg Ala Cys
 85 90 95

Leu Phe Val Pro Ser Ile Asp Val Leu Asn Gln Asn Thr Leu Arg Ile
 100 105 110

Lys Glu Thr Ala Gln Ala Met Ala Gln Leu Ser Arg Trp Asp Arg Gly
 115 120 125

Thr Asn His Leu Leu Phe Asn Met Leu Pro Gly Gly Pro Pro Asp Tyr

619

| | | |
|---|-----|-------------|
| 130 | 135 | 140 |
| Asn Thr Ala Leu Asp Val Pro Arg Asp Arg Ala Leu Leu Ala Gly Gly | | |
| 145 | 150 | 155 160 |
| Gly Phe Ser Thr Trp Thr Tyr Arg Gln Gly Tyr Asp Val Ser Ile Pro | | |
| | 165 | 170 175 |
| Val Tyr Ser Pro Leu Ser Ala Glu Val Asp Leu Pro Glu Lys Gly Pro | | |
| | 180 | 185 190 |
| Gly Pro Arg Gln Tyr Phe Leu Leu Ser Ser Gln Val Gly Leu His Pro | | |
| | 195 | 200 205 |
| Glu Tyr Arg Glu Asp Leu Glu Ala Leu Gln Val Lys His Gly Glu Ser | | |
| | 210 | 215 220 |
| Val Leu Val Leu Asp Lys Cys Thr Asn Leu Ser Glu Gly Val Leu Ser | | |
| | 225 | 230 235 240 |
| Val Arg Lys Arg Cys His Lys His Gln Val Phe Asp Tyr Pro Gln Val | | |
| | 245 | 250 255 |
| Leu Gln Glu Ala Thr Phe Cys Val Val Leu Arg Gly Ala Arg Leu Gly | | |
| | 260 | 265 270 |
| Gln Ala Val Leu Ser Asp Val Leu Gln Ala Gly Cys Val Pro Val Val | | |
| | 275 | 280 285 |
| Ile Ala Asp Ser Tyr Ile Leu Pro Phe Ser Glu Val Leu Asp Trp Lys | | |
| | 290 | 295 300 |
| Arg Ala Ser Val Val Val Pro Glu Glu Lys Met Ser Asp Val Tyr Ser | | |
| | 305 | 310 315 320 |
| Ile Leu Gln Ser Ile Pro Gln Arg Gln Ile Glu Glu Met Gln Arg Gln | | |
| | 325 | 330 335 |
| Ala Arg Trp Phe Trp Glu Ala Tyr Phe Gln Ser Ile Lys Ala Ile Ala | | |
| | 340 | 345 350 |
| Leu Ala Thr Leu Gln Ile Ile Asn Asp Arg Ile Tyr Pro Tyr Ala Ala | | |
| | 355 | 360 365 |
| Ile Ser Tyr Glu Glu Trp Asn Asp Pro Pro Ala Val Lys Trp Gly Ser | | |
| | 370 | 375 380 |
| Val Ser Asn Pro Leu Phe Leu Pro Leu Ile Pro Pro Gln Ser Gln Gly | | |
| | 385 | 390 395 400 |
| Phe Thr Ala Ile Val Leu Thr Tyr Asp Arg Val Glu Ser Leu Phe Arg | | |

620

| | | |
|---|-----|-----|
| 405 | 410 | 415 |
| Val Ile Thr Glu Val Ser Lys Val Pro Ser Leu Ser Lys Leu Leu Val | | |
| 420 | 425 | 430 |
| Val Trp Asn Asn Gln Asn Lys Asn Pro Pro Glu Asp Ser Leu Trp Pro | | |
| 435 | 440 | 445 |
| Lys Ile Arg Val Pro Leu Lys Val Val Arg Thr Ala Glu Asn Lys Leu | | |
| 450 | 455 | 460 |
| Ser Asn Arg Phe Phe Pro Tyr Asp Glu Ile Glu Thr Glu Ala Val Leu | | |
| 465 | 470 | 475 |
| | | 480 |
| Ala Ile Asp Asp Asp Ile Ile Met Leu Thr Ser Asp Glu Leu Gln Phe | | |
| 485 | 490 | 495 |
| Gly Tyr Glu Val Trp Arg Glu Phe Pro Asp Arg Leu Val Gly Tyr Pro | | |
| 500 | 505 | 510 |
| Gly Arg Leu His Leu Trp Asp His Glu Met Asn Lys Trp Lys Tyr Glu | | |
| 515 | 520 | 525 |
| Ser Glu Trp Thr Asn Glu Val Ser Met Val Leu Thr Gly Ala Ala Phe | | |
| 530 | 535 | 540 |
| Tyr His Lys Tyr Phe Asn Tyr Leu Tyr Thr Tyr Lys Met Pro Gly Asp | | |
| 545 | 550 | 555 |
| | | 560 |
| Ile Lys Asn Trp Val Asp Ala His Met Asn Cys Glu Asp Ile Ala Met | | |
| 565 | 570 | 575 |
| Asn Phe Leu Val Ala Asn Val Thr Gly Lys Ala Val Ile Lys Val Thr | | |
| 580 | 585 | 590 |
| Pro Arg Lys Lys Phe Lys Cys Pro Glu Cys Thr Ala Ile Asp Gly Leu | | |
| 595 | 600 | 605 |
| Ser Leu Asp Gln Thr His Met Val Glu Arg Ser Glu Cys Ile Asn Lys | | |
| 610 | 615 | 620 |
| Phe Ala Ser Val Phe Gly Thr Met Pro Leu Lys Val Val Glu His Arg | | |
| 625 | 630 | 635 |
| | | 640 |
| Ala Asp Pro Val Leu Tyr Lys Asp Asp Phe Pro Glu Lys Leu Lys Ser | | |
| 645 | 650 | 655 |
| Phe Pro Asn Ile Gly Ser Leu | | |
| 660 | | |

621

<210> 655

<211> 97

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (38)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (91)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 655

Ala Thr Gln Leu Leu Ser Ser Phe Ser Val Gly Pro Leu Leu Gln Ile
1 5 10 15

Thr Phe Tyr Glu Asp Lys Asn Phe Gln Gly Arg Arg Tyr Asp Cys Asp
20 25 30

Cys Asp Cys Ala Asp Xaa His Thr Tyr Leu Ser Arg Cys Asn Ser Ile
35 40 45

Lys Val Glu Gly Gly Thr Trp Ala Val Tyr Glu Arg Pro Asn Phe Ala
50 55 60

Gly Tyr Met Tyr Ile Leu Pro Gln Gly Glu Tyr Pro Glu Tyr Gln Arg
65 70 75 80

Trp Met Gly Leu Asn Asp Arg Leu Ser Ser Xaa Arg Ala Val Ser Ser
85 90 95

Ala

<210> 656

<211> 167

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (59)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

622

<221> SITE

<222> (73)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 656

Asp Ala Asp Leu Val Ile Trp Asp Pro Asp Ser Val Lys Thr Ile Ser
 1 5 10 15

Ala Lys Thr His Asn Ser Ser Leu Glu Tyr Asn Ile Phe Glu Gly Met
 20 25 30

Glu Cys Arg Gly Ser Pro Leu Val Val Ile Ser Gln Gly Lys Ile Val
 35 40 45

Leu Glu Asp Gly Thr Leu His Val Thr Glu Xaa Ser Gly Arg Tyr Ile
 50 55 60

Pro Arg Lys Pro Phe Pro Asp Phe Xaa Tyr Lys Arg Ile Lys Ala Arg
 65 70 75 80

Ser Arg Leu Ala Glu Leu Arg Gly Val Pro Arg Gly Leu Tyr Asp Gly
 85 90 95

Pro Val Cys Glu Val Ser Val Thr Pro Lys Thr Val Thr Pro Ala Ser
 100 105 110

Ser Ala Lys Thr Ser Pro Ala Lys Gln Gln Ala Pro Pro Val Arg Asn
 115 120 125

Leu His Gln Ser Gly Phe Ser Leu Ser Gly Ala Gln Ile Asp Asp Asn
 130 135 140

Ile Pro Arg Arg Thr Thr Gln Arg Ile Val Ala Pro Pro Gly Gly Arg
 145 150 155 160

Ala Asn Ile Thr Ser Leu Gly
 165

<210> 657

<211> 176

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (6)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (26)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 657

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Xaa | Ser | Leu | Asn | Leu | Xaa | Lys | Leu | Ala | Leu | His | Arg | Gly | Gly | Gly | Arg |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ser | Arg | Thr | Ser | Gly | Ser | Pro | Gly | Leu | Xaa | Glu | Phe | Gly | Thr | Ser | Ala |
| | | 20 | | | | | 25 | | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Leu | Leu | Arg | Leu | Gly | Asp | Glu | Leu | Glu | Met | Ile | Arg | Pro | Ser | Val |
| | 35 | | | | | 40 | | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Tyr | Arg | Asn | Val | Ala | Arg | Gln | Leu | His | Ile | Ser | Leu | Gln | Ser | Glu | Pro |
| 50 | | | | | 55 | | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Val | Thr | Asp | Ala | Phe | Leu | Ala | Val | Ala | Gly | His | Ile | Phe | Ser | Ala |
| 65 | | | | 70 | | | | | | 75 | | | | 80 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Ile | Thr | Trp | Gly | Lys | Val | Val | Ser | Leu | Tyr | Ala | Val | Ala | Ala | Gly |
| | | | 85 | | | | | 90 | | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Ala | Val | Asp | Cys | Val | Arg | Gln | Ala | Gln | Pro | Ala | Met | Val | His | Ala |
| | | 100 | | | | | | 105 | | | | | | 110 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Val | Asp | Cys | Leu | Gly | Glu | Phe | Val | Arg | Lys | Thr | Leu | Ala | Thr | Trp |
| | | 115 | | | | | | 120 | | | | | 125 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Arg | Arg | Arg | Gly | Gly | Trp | Thr | Asp | Val | Leu | Lys | Cys | Val | Val | Ser |
| | 130 | | | | | 135 | | | | | | 140 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Asp | Pro | Gly | Leu | Arg | Ser | His | Trp | Leu | Val | Ala | Ala | Leu | Cys | Ser |
| 145 | | | | | 150 | | | | | 155 | | | | 160 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Phe | Gly | Arg | Phe | Leu | Lys | Ala | Ala | Phe | Phe | Val | Leu | Leu | Pro | Glu | Arg |
| | | | 165 | | | | | | 170 | | | | | 175 | |

<210> 658

<211> 137

<212> PRT

<213> Homo sapiens

<220>
<221> SITE
<222> (75)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (91)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (101)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (124)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (129)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (131)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 658
Gly Pro Val Gly Ser Ser Ser Glu Ala Pro Arg Gly Ala Gly Asp Ala
1 5 10 15
Gly Met Ala Gly Glu Leu Thr Pro Glu Glu Ala Gln Tyr Lys Lys
20 25 30
Ala Phe Ser Ala Val Asp Thr Asp Gly Asn Gly Thr Ile Asn Ala Gln
35 40 45
Glu Leu Gly Ala Ala Leu Lys Ala Thr Gly Lys Asn Leu Ser Glu Ala
50 55 60
Gln Leu Arg Lys Leu Ile Ser Glu Val Asp Xaa Asp Gly Asp Gly Glu
65 70 75 80
Ile Ser Phe Gln Glu Phe Leu Thr Ala Ala Xaa Lys Ala Arg Ala Gly
85 90 95

625

Leu Glu Asp Leu Xaa Val Ala Phe Arg Ala Phe Asp Gln Asp Gly Asp
 100 105 110

Gly His Ile Thr Val Asp Glu Leu Arg Arg Ala Xaa Ala Gly Leu Gly
 115 120 125

Xaa Leu Xaa Glu Ile Asp His Phe Gly
 130 135

<210> 659
 <211> 34
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (2)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (28)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (30)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 659
 Pro Xaa Ser Arg Gln Asp Val Met Asp Ile Val Phe Ile Glu Gln Leu
 1 5 10 15

Ser Val Ile Thr Thr Ile Gly Val Tyr Asp Trp Xaa Gln Xaa Ser Asn
 20 25 30

Arg Ser

<210> 660
 <211> 56
 <212> PRT
 <213> Homo sapiens

<400> 660
 Asn Pro Ile Ser Pro Lys Asn Tyr Lys Lys Ile Ser Gln Ala Gln Ser
 1 5 10 15

626

Gln Leu Pro Val Ile Pro Ala Thr Gln Glu Ala Glu Ser Gly Glu Ser
20 25 30

Leu Gly Pro Gly Ala Ala Glu Val Asn Ser Glu Pro Arg Leu His His
35 40 45

Arg Thr Pro Ala Trp Ile Thr Lys
50 55

<210> 661
<211> 41
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (31)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (36)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (39)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 661
Tyr Ile Gly Phe Val Ile Leu Val Phe Phe Ala Ser Ser Tyr Val Lys
1 5 10 15

Glu Ile Asp Asn Lys Ile Leu Asn Asn Lys Lys Lys Xaa Lys Xaa Ser
20 25 30

Ser Lys Gly Xaa Val Ala Xaa Ala Ile
35 40

<210> 662
<211> 524

627

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (124)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (191)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 662

Cys Glu Ala Trp Arg Gly Arg Ala Asp Pro Gly Gly Gln Ser Cys Leu
 1 5 10 15

Gln Ala Leu Gln Asn Ser Thr Ala Pro Gln His Pro Gly Leu His Arg
 20 25 30

Trp Thr Gly Asp Arg Lys Met Pro Pro Arg Arg Asp Arg Gly Cys Asp
 35 40 45

Pro Val Gly Asn Ile Pro Gln Gly Glu Ser Gly Gly Trp Trp Pro Glu
 50 55 60

Gly Ala Gly Asp Leu Leu Gly Ala Thr Pro Asp Arg Glu Ser Pro Gln
 65 70 75 80

Leu Pro Gly Gln Arg Leu Gln Pro His Pro Gln Gln Cys Leu His Gly
 85 90 95

Arg Arg Val Arg Gly Pro Ser Trp Arg Val Glu Ala Trp Gly Pro Gly
 100 105 110

Leu His Val Phe Gly Pro Gly Gln Arg Trp Gly Xaa Ser Pro Gln Gly
 115 120 125

Ile Pro Glu Leu Glu Gln Tyr Asp Pro Pro Glu Leu Ala Asp Ser Ser
 130 135 140

Gly Arg Val Val Arg Glu Lys Trp Ser Ala Asp Met Trp Arg Leu Gly
 145 150 155 160

Cys Leu Ile Trp Glu Val Phe Asn Gly Pro Leu Pro Arg Ala Ala Ala
 165 170 175

Leu Arg Asn Pro Gly Lys Ile Pro Lys Thr Leu Val Pro His Xaa Cys
 180 185 190

Lys Leu Val Gly Ala Asn Pro Lys Val Arg Pro Asn Pro Ala Arg Phe

628

| 195 | 200 | 205 |
|--|-----|---------|
| Leu Gln Asn Cys Arg Ala Pro Gly Gly Phe Met Ser Asn Arg Phe Val 210 | 215 | 220 |
| Glu Thr Asn Leu Phe Leu Glu Glu Ile Gln Ile Lys Glu Pro Ala Glu 225 | 230 | 235 240 |
| Lys Gln Lys Phe Phe Gln Glu Leu Ser Lys Ser Leu Asp Ala Phe Pro 245 | 250 | 255 |
| Glu Asp Phe Cys Arg His Lys Val Leu Pro Gln Leu Leu Thr Ala Phe 260 | 265 | 270 |
| Glu Phe Gly Asn Ala Gly Ala Val Val Leu Thr Pro Leu Phe Lys Val 275 | 280 | 285 |
| Gly Lys Phe Leu Ser Ala Glu Glu Tyr Gln Gln Lys Ile Ile Pro Val 290 | 295 | 300 |
| Val Val Lys Met Phe Ser Ser Thr Asp Arg Ala Met Arg Ile Arg Leu 305 | 310 | 315 320 |
| Leu Gln Gln Met Glu Gln Phe Ile Gln Tyr Leu Asp Glu Pro Thr Val 325 | 330 | 335 |
| Asn Thr Gln Ile Phe Pro His Val Val His Gly Phe Leu Asp Thr Asn 340 | 345 | 350 |
| Pro Ala Ile Arg Glu Gln Thr Val Lys Ser Met Leu Leu Leu Ala Pro 355 | 360 | 365 |
| Lys Leu Asn Glu Ala Asn Leu Asn Val Glu Leu Met Lys His Phe Ala 370 | 375 | 380 |
| Arg Leu Gln Ala Lys Asp Glu Gln Gly Pro Ile Arg Cys Asn Thr Thr 385 | 390 | 395 400 |
| Val Cys Leu Gly Lys Ile Gly Ser Tyr Leu Ser Ala Ser Thr Arg His 405 | 410 | 415 |
| Arg Val Leu Thr Ser Ala Phe Ser Arg Ala Thr Arg Asp Pro Phe Ala 420 | 425 | 430 |
| Pro Ser Arg Val Ala Gly Val Leu Gly Phe Ala Ala Thr His Asn Leu 435 | 440 | 445 |
| Tyr Ser Met Asn Asp Cys Ala Gln Lys Ile Leu Pro Val Leu Cys Gly 450 | 455 | 460 |
| Leu Thr Val Asp Pro Glu Lys Ser Val Arg Asp Gln Ala Phe Lys Ala | | |

```
<220>
<221> SITE
<222> (29)
<223> Xaa equals any of the naturally occurring L-amino acids
```

Trp Arg Val Asp Pro Pro Phe Arg Pro Cys Leu Gln Ser Glu Glu Asp
130 135 140

630

Val Ser Gln Phe Asp Thr Arg Phe Thr Arg Gln Thr Pro Val Asp Ser
 145 150 155 160

Pro Asp Asp Thr Ala Leu Ser Glu Ser Ala Asn Gln Ala Phe Leu Gly
 165 170 175

Phe Thr Tyr Val Ala Pro Ser Val Leu Asp Ser Ile Lys Glu Gly Phe
 180 185 190

Ser Phe Gln Pro Lys Leu Arg Ser Pro Arg Arg Leu Asn Ser Ser Pro
 195 200 205

Arg Ala Pro Val Ser Pro Leu Lys Phe Ser Pro Phe Glu Gly Phe Arg
 210 215 220

Pro Ser Pro Ser Leu Pro Glu Pro Thr Glu Leu Pro Leu Pro Pro Leu
 225 230 235 240

Leu Pro Pro Pro Pro Pro Ser Thr Thr Ala Pro Leu Pro Ile Arg Pro
 245 250 255

Pro Ser Gly Thr Lys Lys Ser Lys Arg Gly Arg Gly Arg Pro Gly Arg
 260 265 270

<210> 664

<211> 256

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (99)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 664

Gly Thr Arg Arg Glu Thr Trp Arg Pro Gly Ser Met Ala Gly Leu Glu
 1 5 10 15

Leu Leu Ser Asp Gln Gly Tyr Arg Val Asp Gly Arg Arg Ala Gly Glu
 20 25 30

Leu Arg Lys Ile Gln Ala Arg Met Gly Val Phe Ala Gln Ala Asp Gly
 35 40 45

Ser Ala Tyr Ile Glu Gln Gly Asn Thr Lys Ala Leu Ala Val Val Tyr
 50 55 60

631

Gly Pro His Glu Ile Arg Gly Ser Arg Ala Arg Ala Leu Pro Asp Arg
65 70 75 80

Ala Leu Val Asn Cys Gln Tyr Ser Ser Ala Thr Phe Ser Thr Gly Glu
85 90 95

Arg Lys Xaa Arg Pro His Gly Asp Arg Lys Ser Cys Glu Met Gly Leu
100 105 110

Gln Leu Arg Gln Thr Phe Glu Ala Ala Ile Leu Thr Gln Leu His Pro
115 120 125

Arg Ser Gln Ile Asp Ile Tyr Val Gln Val Leu Gln Ala Asp Gly Gly
130 135 140

Thr Tyr Ala Ala Cys Val Asn Ala Ala Thr Leu Ala Val Leu Asp Ala
145 150 155 160

Gly Ile Pro Met Arg Asp Phe Val Cys Ala Cys Ser Ala Gly Phe Val
165 170 175

Asp Gly Thr Ala Leu Ala Asp Leu Ser His Val Glu Glu Ala Ala Gly
180 185 190

Gly Pro Gln Leu Ala Leu Ala Leu Leu Pro Ala Ser Gly Gln Ile Ala
195 200 205

Leu Leu Glu Met Asp Ala Arg Leu His Glu Asp His Leu Glu Arg Val
210 215 220

Leu Glu Ala Ala Ala Gln Ala Ala Arg Asp Val His Thr Leu Leu Asp
225 230 235 240

Arg Val Val Arg Gln His Val Arg Glu Ala Ser Ile Leu Leu Gly Asp
245 250 255

<210> 665

<211> 241

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (9)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (122)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 665

Pro Arg Gly Asp Lys Ala Arg Thr Xaa Pro Pro Ala Ala Ser Ala Arg
1 5 10 15

Pro Ser Arg Ser Lys Arg Gly Gly Glu Glu Arg Val Leu Glu Lys Glu
20 25 30

Glu Glu Glu Asp Asp Asp Glu Asp Glu Asp Glu Glu Asp Asp Val Ser
35 40 45

Glu Gly Ser Glu Val Pro Glu Ser Asp Arg Pro Ala Gly Ala Gln His
50 55 60

His Gln Leu Asn Gly Glu Arg Gly Pro Gln Ser Ala Lys Glu Arg Val
65 70 75 80

Lys Glu Trp Thr Pro Cys Gly Pro His Gln Gly Gln Asp Glu Gly Arg
85 90 95

Gly Pro Ala Pro Gly Ser Gly Thr Arg Gln Val Phe Ser Met Ala Ala
100 105 110

Met Asn Lys Glu Gly Gly Thr Ala Ser Xaa Ala Thr Gly Pro Asp Ser
115 120 125

Pro Ser Pro Val Pro Leu Pro Pro Gly Lys Pro Ala Leu Pro Gly Ala
130 135 140

Asp Gly Thr Pro Phe Gly Cys Pro Pro Gly Arg Lys Glu Lys Pro Ser
145 150 155 160

Asp Pro Val Glu Trp Thr Val Met Asp Val Val Glu Tyr Phe Thr Glu
165 170 175

Ala Gly Phe Pro Glu Gln Ala Thr Val Phe Gln Glu Gln Glu Ile Asp
180 185 190

Gly Lys Ser Leu Leu Leu Met Gln Arg Thr Asp Val Leu Thr Gly Leu
195 200 205

Ser Ile Arg Leu Gly Pro Ala Leu Lys Ile Tyr Glu His His Ile Lys
210 215 220

Val Leu Gln Gln Gly His Phe Glu Asp Asp Asp Pro Asp Gly Phe Leu
225 230 235 240

633

Gly

<210> 666
<211> 131
<212> PRT
<213> Homo sapiens

<400> 666

Val Thr Gly Gly Gly Ala Val Val Leu Gly Ala Glu Ser His Ala Ser
1 5 10 15

Lys Asp Val Ala Ile Asp Met Met Asp Ser Arg Thr Ser Gln Gln Leu
20 25 30

Gln Leu Ile Asp Glu Gln Asp Ser Tyr Ile Gln Ser Arg Ala Asp Thr
35 40 45

Met Gln Asn Ile Glu Ser Thr Ile Val Glu Leu Gly Ser Ile Phe Gln
50 55 60

Gln Leu Ala His Met Val Lys Glu Gln Glu Glu Thr Ile Gln Arg Ile
65 70 75 80

Asp Glu Asn Val Leu Gly Ala Gln Leu Asp Val Glu Ala Ala His Ser
85 90 95

Glu Ile Leu Lys Tyr Phe Gln Ser Val Thr Ser Asn Arg Trp Leu Met
100 105 110

Val Lys Ile Phe Leu Ile Leu Ile Val Phe Phe Ile Ile Phe Val Val
115 120 125

Phe Leu Ala
130

<210> 667
<211> 652
<212> PRT
<213> Homo sapiens

<400> 667

Leu Ser Trp Asn Arg Tyr Thr Ser Val Ser Pro Leu His Arg Ser Leu
1 5 10 15

Gln Leu Pro Pro Arg Val Ser Gly Val Arg Cys Asp Gln Cys Ala Arg

634

| | | |
|---|-----|---------|
| 20 | 25 | 30 |
| Gly Phe Ser Gly Ile Phe Pro Ala Cys His Pro Cys His Ala Cys Phe | | |
| 35 | 40 | 45 |
| Gly Asp Trp Asp Arg Val Val Gln Asp Leu Ala Ala Arg Thr Gln Arg | | |
| 50 | 55 | 60 |
| Leu Glu Gln Arg Ala Gln Glu Leu Gln Gln Thr Gly Val Leu Gly Ala | | |
| 65 | 70 | 75 80 |
| Phe Glu Ser Ser Phe Trp His Met Gln Glu Lys Leu Gly Ile Val Gln | | |
| 85 | 90 | 95 |
| Gly Ile Val Gly Ala Arg Asn Thr Ser Ala Ala Ser Thr Ala Gln Leu | | |
| 100 | 105 | 110 |
| Val Glu Ala Thr Glu Glu Leu Arg Arg Glu Ile Gly Glu Ala Thr Glu | | |
| 115 | 120 | 125 |
| His Leu Thr Gln Leu Glu Ala Asp Leu Thr Asp Val Gln Asp Glu Asn | | |
| 130 | 135 | 140 |
| Phe Asn Ala Asn His Ala Leu Ser Gly Leu Glu Arg Asp Arg Leu Ala | | |
| 145 | 150 | 155 160 |
| Leu Asn Leu Thr Leu Arg Gln Leu Asp Gln His Leu Asp Leu Leu Lys | | |
| 165 | 170 | 175 |
| His Ser Asn Phe Leu Gly Ala Tyr Asp Ser Ile Arg His Ala His Ser | | |
| 180 | 185 | 190 |
| Gln Ser Ala Glu Ala Glu Arg Arg Ala Asn Thr Ser Ala Leu Ala Val | | |
| 195 | 200 | 205 |
| Pro Ser Pro Val Ser Asn Ser Ala Ser Ala Arg His Arg Thr Glu Ala | | |
| 210 | 215 | 220 |
| Leu Met Asp Ala Gln Lys Glu Asp Phe Asn Ser Lys His Met Ala Asn | | |
| 225 | 230 | 235 240 |
| Gln Arg Ala Leu Gly Lys Leu Ser Ala His Thr His Thr Leu Ser Leu | | |
| 245 | 250 | 255 |
| Thr Asp Ile Asn Glu Leu Val Cys Gly Ala Pro Gly Asp Ala Pro Cys | | |
| 260 | 265 | 270 |
| Ala Thr Ser Pro Cys Gly Gly Ala Gly Cys Arg Asp Glu Asp Gly Gln | | |
| 275 | 280 | 285 |
| Pro Arg Cys Gly Gly Leu Ser Cys Asn Gly Ala Ala Ala Thr Ala Asp | | |

635

290 295 300

Leu Ala Leu Gly Arg Ala Arg His Thr Gln Ala Glu Leu Gln Arg Ala
305 310 315 320

Leu Ala Glu Gly Gly Ser Ile Leu Ser Arg Val Ala Glu Thr Arg Arg
 325 330 335

Gln Ala Ser Glu Ala Gln Gln Arg Ala Gln Ala Ala Leu Asp Lys Ala
 340 345 350

Asn Ala Ser Arg Gly Gln Val Glu Gln Ala Asn Gln Glu Leu Gln Glu
 355 360 365

Leu Ile Gln Ser Val Lys Asp Phe Leu Asn Gln Glu Gly Ala Asp Pro
370 375 380

Asp Ser Ile Glu Met Val Ala Thr Arg Val Leu Glu Leu Ser Ile Pro
385 390 395 400

Ala Ser Ala Glu Gln Ile Gln His Leu Ala Gly Ala Ile Ala Glu Arg
 405 410 415

Val Arg Ser Leu Ala Asp Val Asp Ala Ile Leu Ala Arg Thr Val Gly
420 425 430

Asp Val Arg Arg Ala Glu Gln Leu Leu Gln Asp Ala Arg Arg Ala Arg
435 440 445

Ser Trp Ala Glu Asp Glu Lys Gln Lys Ala Glu Thr Val Gln Ala Ala
450 455 460

Leu Glu Glu Ala Gln Arg Ala Gln Gly Ile Ala Gln Gly Ala Ile Arg
465 470 475 480

Gly Ala Val Ala Asp Thr Arg Asp Thr Glu Gln Thr Leu Tyr Gln Val
 485 490 495

Gln Glu Arg Met Ala Gly Ala Glu Arg Ala Leu Ser Ser Ala Gly Glu
500 505 510

Arg Ala Arg Gln Leu Asp Ala Leu Leu Glu Ala Leu Lys Leu Lys Arg
515 520 525

Ala Gly Asn Ser Leu Ala Ala Ser Thr Ala Glu Glu Thr Ala Gly Ser
530 535 540

Ala Gln Gly Arg Ala Gln Glu Ala Glu Gln Leu Leu Arg Gly Pro Leu
545 550 555 560

Gly Asp Gln Tyr Gln Thr Val Lys Ala Leu Ala Glu Arg Lys Ala Gln

565

575

Asp Glu Pro Gln Arg Leu Gln Phe Pro Leu Pro Thr Ala Gln Arg Ser
100 105 110

637

Leu Glu Pro Gly Thr Pro Arg Trp Ala Asn Tyr Val Lys Gly Val Ile
115 120 125

Gln Tyr Tyr Pro Ala Ala Pro Leu Pro Gly Phe Ser Ala Val Val Val
130 135 140

Ser Ser Val Pro Leu Gly Gly Gly Leu Ser Ser Ser Ala Ser Leu Glu
145 150 155 160

Val Ala Thr Tyr Thr Phe Leu Gln Gln Leu Cys Pro Asp Ser Gly Thr
165 170 175

Ile Ala Ala Arg Ala Gln Val Cys Gln Gln Ala Glu His Ser Phe Ala
180 185 190

Gly Met Pro Cys Gly Ile Met Asp Gln Phe Ile Ser Leu Met Gly Gln
195 200 205

Lys Gly His Ala Leu Leu Ile Asp Cys Arg Ser Leu Glu Thr Ser Leu
210 215 220

Val Pro Leu Ser Asp Pro Lys Leu Ala Val Leu Ile Thr Asn Ser Asn
225 230 235 240

Val Arg His Ser Leu Ala Ser Ser Glu Tyr Pro Val Arg Arg Arg Gln
245 250 255

Cys Glu Glu Val Ala Arg Ala Leu Gly Lys Glu Ser Leu Arg Glu Val
260 265 270

Gln Leu Glu Glu Leu Glu Ala Ala Arg Asp Leu Val Ser Lys Glu Gly
275 280 285

Phe Arg Arg Ala Arg His Val Val Gly Glu Ile Arg Arg Thr Ala Gln
290 295 300

Ala Ala Ala Ala Leu Arg Arg Gly Asp Tyr Arg Ala Phe Gly Arg Leu
305 310 315 320

Met Val Glu Ser His Arg Ser Leu Arg Asp Asp Tyr Glu Val Ser Cys
325 330 335

Pro Glu Leu Asp Gln Leu Val Glu Ala Ala Leu Ala Val Pro Gly Val
340 345 350

Tyr Gly Ser Arg Met Thr Gly Gly Gly Phe Gly Gly Cys Thr Val Thr
355 360 365

Leu Leu Glu Ala Ser Ala Ala Pro His Ala Met Arg His Ile Gln Glu
370 375 380

638

His Tyr Gly Gly Thr Ala Thr Phe Tyr Leu Ser Gln Ala Ala Asp Gly
 385 390 395 400

Ala Lys Val Leu Cys Leu
 405

<210> 669
 <211> 86
 <212> PRT
 <213> Homo sapiens

<400> 669
 Pro Glu Pro Thr Val Val Met Ala Ala Arg Ala Leu Cys Met Leu Gly
 1 5 10 15
 Leu Val Leu Ala Leu Leu Ser Ser Ser Ser Ala Glu Glu Tyr Val Gly
 20 25 30
 Leu Ser Ala Asn Gln Cys Ala Val Pro Ala Lys Asp Arg Val Asp Cys
 35 40 45
 Gly Tyr Pro His Val Thr Pro Lys Glu Cys Asn Asn Arg Gly Cys Cys
 50 55 60
 Phe Asp Ser Arg Ile Pro Gly Val Pro Trp Cys Phe Lys Pro Leu Gln
 65 70 75 80
 Glu Ala Glu Cys Thr Phe
 85

<210> 670
 <211> 392
 <212> PRT
 <213> Homo sapiens
 <220>
 <221> SITE
 <222> (6)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 670
 Gly Gly Gly Ala Arg Xaa Ser Pro Ala Thr Gln Pro Pro Pro Leu Leu
 1 5 10 15
 Pro Pro Ser Ala Thr Gly Pro Asp Ala Thr Val Gly Gly Pro Ala Pro
 20 25 30

Thr Pro Leu Leu Pro Pro Ser Ala Thr Ala Ser Val Lys Met Glu Pro
 35 40 45
 Glu Asn Lys Tyr Leu Pro Glu Leu Met Ala Glu Lys Asp Ser Leu Asp
 50 55 60
 Pro Ser Phe Thr His Ala Met Gln Leu Leu Thr Ala Glu Ile Glu Lys
 65 70 75 80
 Ile Gln Lys Gly Asp Ser Lys Lys Asp Asp Glu Glu Asn Tyr Leu Asp
 85 90 95
 Leu Phe Ser His Lys Asn Met Lys Leu Lys Glu Arg Val Leu Ile Pro
 100 105 110
 Val Lys Gln Tyr Pro Lys Phe Asn Phe Val Gly Lys Ile Leu Gly Pro
 115 120 125
 Gln Gly Asn Thr Ile Lys Arg Leu Gln Glu Glu Thr Gly Ala Lys Ile
 130 135 140
 Ser Val Leu Gly Lys Gly Ser Met Arg Asp Lys Ala Lys Glu Glu Glu
 145 150 155 160
 Leu Arg Lys Gly Gly Asp Pro Lys Tyr Ala His Leu Asn Met Asp Leu
 165 170 175
 His Val Phe Ile Glu Val Phe Gly Pro Pro Cys Glu Ala Tyr Ala Leu
 180 185 190
 Met Ala His Ala Met Glu Glu Val Lys Lys Phe Leu Val Pro Asp Met
 195 200 205
 Met Asp Asp Ile Cys Gln Glu Gln Phe Leu Glu Leu Ser Tyr Leu Asn
 210 215 220
 Gly Val Pro Glu Pro Ser Arg Gly Arg Gly Val Pro Val Arg Gly Arg
 225 230 235 240
 Gly Ala Ala Pro Pro Pro Pro Pro Val Pro Arg Gly Arg Gly Val Gly
 245 250 255
 Pro Pro Arg Gly Ala Leu Val Arg Gly Thr Pro Val Arg Gly Ala Ile
 260 265 270
 Thr Arg Gly Ala Thr Val Thr Arg Gly Val Pro Pro Pro Pro Thr Val
 275 280 285
 Arg Gly Ala Pro Ala Pro Arg Ala Arg Thr Ala Gly Ile Gln Arg Ile
 290 295 300

640

Pro Leu Pro Pro Pro Pro Ala Pro Glu Thr Tyr Glu Glu Tyr Gly Tyr
305 310 315 320

Asp Asp Thr Tyr Ala Glu Gln Ser Tyr Glu Gly Tyr Glu Gly Tyr Tyr
325 330 335

Ser Gln Ser Gln Gly Asp Ser Glu Tyr Tyr Asp Tyr Gly His Gly Glu
340 345 350

Val Gln Asp Ser Tyr Glu Ala Tyr Gly Gln Asp Asp Trp Asn Gly Thr
355 360 365

Arg Pro Ser Leu Lys Ala Pro Pro Ala Arg Pro Val Lys Gly Ala Tyr
370 375 380

Arg Glu His Pro Tyr Gly Arg Tyr
385 390

<210> 671

<211> 180

<212> PRT

<213> Homo sapiens

<400> 671

Arg Asn Met Ser Ser Phe Ser Arg Ala Pro Gln Gln Trp Ala Thr Phe
1 5 10 15

Ala Arg Ile Trp Tyr Leu Leu Asp Gly Lys Met Gln Pro Pro Gly Lys
20 25 30

Leu Ala Ala Met Ala Ser Ile Arg Leu Gln Gly Leu His Lys Pro Val
35 40 45

Tyr His Ala Leu Ser Asp Cys Gly Asp His Val Val Ile Met Asn Thr
50 55 60

Arg His Ile Ala Phe Ser Gly Asn Lys Trp Glu Gln Lys Val Tyr Ser
65 70 75 80

Ser His Thr Gly Tyr Pro Gly Gly Phe Arg Gln Val Thr Ala Ala Gln
85 90 95

Leu His Leu Arg Asp Pro Val Ala Ile Val Lys Leu Ala Ile Tyr Gly
100 105 110

Met Leu Pro Lys Asn Leu His Arg Arg Thr Met Met Glu Arg Leu His
115 120 125

Leu Phe Pro Asp Glu Tyr Ile Pro Glu Asp Ile Leu Lys Asn Leu Val

641

130 135 140
Glu Glu Leu Pro Gln Pro Arg Lys Ile Pro Lys Arg Leu Asp Glu Tyr
145 150 155 160
Thr Gln Glu Glu Ile Asp Ala Phe Pro Arg Leu Trp Thr Pro Pro Glu
165 170 175
Asp Tyr Arg Leu
180

<210> 672
<211> 78
<212> PRT
<213> Homo sapiens

<400> 672
Glu Asn Tyr Gln Phe Thr Tyr Arg Arg Phe Phe Phe Pro Asn Ser Arg
1 5 10 15
Phe His Pro Arg Pro Phe Glu Glu Leu Gln Thr Leu Ser Leu Arg Lys
20 25 30
Glu Arg Gly Gln Pro Lys Ile Asn Ala Lys Phe Ala Tyr Thr Pro Ser
35 40 45
His Ser Asp Val Leu Val Val Thr Tyr Tyr Gln Cys Gly Arg Glu Pro
50 55 60
Lys Leu His Phe Arg Ser Lys Tyr Ser Leu Cys Arg Tyr Cys
65 70 75

<210> 673
<211> 139
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (113)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (132)
<223> Xaa equals any of the naturally occurring L-amino acids

642

<400> 673

Pro Thr Arg Pro Pro Leu Cys Arg Gly Ala Ala Ser Arg Gly Leu Leu
1 5 10 15

Cys Lys Trp Ala Pro Trp Pro Ser Ala Pro Val Pro Ala Thr Arg Asp
20 25 30

Arg Ala Pro Arg Pro Ala Arg Gly Arg Arg Pro Gly Arg Leu Gly Ser
35 40 45

Thr Ser Ser Asn Ser Ser Cys Ser Ser Thr Glu Cys Pro Gly Glu Ala
50 55 60

Ile Pro His Pro Pro Gly Leu Pro Lys Ala Asp Pro Gly His Trp Trp
65 70 75 80

Ala Ser Phe Phe Phe Gly Lys Ser Thr Leu Pro Phe Met Ala Thr Val
85 90 95

Leu Glu Ser Ala Glu His Ser Glu Pro Pro Gln Ala Ser Ser Ser Met
100 105 110

Xaa Ala Cys Gly Leu Ala Arg Glu Ala Pro Arg Lys Gln Pro Gly Gly
115 120 125

Gln Ser Ser Xaa Ala Ser Ala Gly Pro Pro Ser
130 135

<210> 674

<211> 279

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (58)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (193)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 674

643

Glu Arg Ala His Ser Leu Xaa His Gly Val Asp Gly Glu Pro Cys Pro
 1 5 10 15
 Glu Asp Tyr Lys Tyr Ile Ser Glu Asn Cys Glu Thr Ser Thr Met Asn
 20 25 30
 Ile Asp Arg Asn Ile Thr His Leu Gln His Cys Thr Phe Val Asp Asp
 35 40 45
 Cys Ser Ser Ser Asn Cys Leu Cys Gly Xaa Phe Ser Ile Arg Cys Trp
 50 55 60
 Tyr Asp Lys Asp Gly Arg Leu Leu Gln Glu Phe Asn Lys Ile Glu Pro
 65 70 75 80
 Pro Leu Ile Phe Glu Cys Asn Gln Ala Cys Ser Cys Trp Arg Asn Cys
 85 90 95
 Lys Asn Arg Val Val Gln Ser Gly Ile Lys Val Arg Leu Gln Leu Tyr
 100 105 110
 Arg Thr Ala Lys Met Gly Trp Gly Val Arg Ala Leu Gln Thr Ile Pro
 115 120 125
 Gln Gly Thr Phe Ile Cys Glu Tyr Val Gly Glu Leu Ile Ser Asp Ala
 130 135 140
 Glu Ala Asp Val Arg Glu Asp Asp Ser Tyr Leu Phe Asp Leu Asp Asn
 145 150 155 160
 Lys Asp Gly Glu Val Tyr Cys Ile Asp Ala Arg Tyr Tyr Gly Asn Ile
 165 170 175
 Ser Arg Phe Ile Asn His Leu Cys Asp Pro Asn Ile Ile Pro Val Arg
 180 185 190
 Xaa Phe Met Leu His Gln Asp Leu Arg Phe Pro Arg Ile Ala Phe Phe
 195 200 205
 Ser Ser Arg Asp Ile Arg Thr Gly Glu Glu Leu Gly Phe Asp Tyr Gly
 210 215 220
 Asp Arg Phe Trp Asp Ile Lys Ser Lys Tyr Phe Thr Cys Gln Cys Gly
 225 230 235 240
 Ser Glu Lys Cys Lys His Ser Ala Glu Ala Ile Ala Leu Glu Gln Ser
 245 250 255
 Arg Leu Ala Arg Leu Asp Pro His Pro Glu Leu Leu Pro Glu Leu Gly
 260 265 270

644

Ser Leu Pro Pro Val Asn Thr
275

<210> 675
<211> 405
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (393)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (394)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 675
Arg Asn Thr Leu Gly Arg Gly Thr Thr Ile Thr Leu Val Leu Lys Glu
1 5 10 15
Glu Ala Ser Asp Tyr Leu Glu Leu Asp Thr Ile Lys Asn Leu Val Lys
20 25 30
Lys Tyr Ser Gln Phe Ile Asn Phe Pro Ile Tyr Val Trp Ser Ser Lys
35 40 45
Thr Glu Thr Val Glu Glu Pro Met Glu Glu Glu Glu Ala Ala Lys Glu
50 55 60
Glu Lys Glu Glu Ser Asp Asp Glu Ala Ala Val Glu Glu Glu Glu
65 70 75 80
Glu Lys Lys Pro Lys Thr Lys Lys Val Glu Lys Thr Val Trp Asp Trp
85 90 95
Glu Leu Met Asn Asp Ile Lys Pro Ile Trp Gln Arg Pro Ser Lys Glu
100 105 110
Val Glu Glu Asp Glu Tyr Lys Ala Phe Tyr Lys Ser Phe Ser Lys Glu
115 120 125
Ser Asp Asp Pro Met Ala Tyr Ile His Phe Thr Ala Glu Gly Glu Val
130 135 140
Thr Phe Lys Ser Ile Leu Phe Val Pro Thr Ser Ala Pro Arg Gly Leu
145 150 155 160

645

Phe Asp Glu Tyr Gly Ser Lys Lys Ser Asp Tyr Ile Lys Leu Tyr Val
 165 170 175
 Arg Arg Val Phe Ile Thr Asp Asp Phe His Asp Met Met Pro Lys Tyr
 180 185 190
 Leu Asn Phe Val Lys Gly Val Val Asp Ser Asp Asp Leu Pro Leu Asn
 195 200 205
 Val Ser Arg Glu Thr Leu Gln Gln His Lys Leu Leu Lys Val Ile Arg
 210 215 220
 Lys Lys Leu Val Arg Lys Thr Leu Asp Met Ile Lys Lys Ile Ala Asp
 225 230 235 240
 Asp Lys Tyr Asn Asp Thr Phe Trp Lys Glu Phe Gly Thr Asn Ile Lys
 245 250 255
 Leu Gly Val Ile Glu Asp His Ser Asn Arg Thr Arg Leu Ala Lys Leu
 260 265 270
 Leu Arg Phe Gln Ser Ser His His Pro Thr Asp Ile Thr Ser Leu Asp
 275 280 285
 Gln Tyr Val Glu Arg Met Lys Glu Lys Gln Asp Lys Ile Tyr Phe Met
 290 295 300
 Ala Gly Ser Ser Arg Lys Glu Ala Glu Ser Ser Pro Phe Val Glu Arg
 305 310 315 320
 Leu Leu Lys Lys Gly Tyr Glu Val Ile Tyr Leu Thr Glu Pro Val Asp
 325 330 335
 Glu Tyr Cys Ile Gln Ala Leu Pro Glu Phe Asp Gly Lys Arg Phe Gln
 340 345 350
 Asn Val Ala Lys Glu Gly Val Lys Phe Asp Glu Ser Glu Lys Thr Lys
 355 360 365
 Glu Ser Arg Glu Ala Val Glu Lys Glu Phe Glu Pro Leu Leu Asn Trp
 370 375 380
 Met Lys Asp Lys Ala Leu Lys Gly Xaa Xaa Leu Trp Glu Ile Leu Pro
 385 390 395 400
 Ile Cys Gly Lys Tyr
 405

<210> 676

646

<211> 465
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (5)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (6)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (16)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 676
Asn Asp Ser Leu Xaa Xaa Lys Ala Gly Thr Pro Ala Gly Asn Arg Xaa
1 5 10 15

Gly Ile Pro Gly Ser Thr His Ala Ser Ala Ala Ala Pro Phe Ala Ala
20 25 30

Ala Leu Ala Arg Asp Pro Asn Pro Ala Ser Pro Leu Pro Glu His Arg
35 40 45

Pro Arg Leu His Arg Gly Pro Gly Pro Pro Ala Arg Leu Ala Ala Ala
50 55 60

Met Ala Asp Pro Lys Tyr Ala Asp Leu Pro Gly Ile Ala Arg Asn Glu
65 70 75 80

Pro Asp Val Tyr Glu Thr Ser Asp Leu Pro Glu Asp Asp Gln Ala Glu
85 90 95

Phe Asp Ala Glu Glu Leu Thr Ser Thr Ser Val Glu His Ile Ile Val
100 105 110

Asn Pro Asn Ala Ala Tyr Asp Lys Phe Lys Asp Lys Arg Val Gly Thr
115 120 125

Lys Gly Leu Asp Phe Ser Asp Arg Ile Gly Lys Thr Lys Arg Thr Gly
130 135 140

Tyr Glu Ser Gly Glu Tyr Glu Met Leu Gly Glu Gly Leu Gly Val Lys
145 150 155 160

Glu Thr Pro Gln Gln Lys Tyr Gln Arg Leu Leu His Glu Val Gln Glu

647

| | | |
|---|-----|-----|
| 165 | 170 | 175 |
| Leu Thr Thr Glu Val Glu Lys Ile Lys Thr Thr Val Lys Glu Ser Ala | | |
| 180 | 185 | 190 |
| Thr Glu Glu Lys Leu Thr Pro Val Leu Leu Ala Lys Gln Leu Ala Ala | | |
| 195 | 200 | 205 |
| Leu Lys Gln Gln Leu Val Ala Ser His Leu Glu Lys Leu Leu Gly Pro | | |
| 210 | 215 | 220 |
| Asp Ala Ala Ile Asn Leu Thr Asp Pro Asp Gly Ala Leu Ala Lys Arg | | |
| 225 | 230 | 240 |
| Leu Leu Leu Gln Leu Glu Ala Thr Lys Asn Ser Lys Gly Gly Ser Gly | | |
| 245 | 250 | 255 |
| Gly Lys Thr Thr Gly Thr Pro Pro Asp Ser Ser Leu Val Thr Tyr Glu | | |
| 260 | 265 | 270 |
| Leu His Ser Arg Pro Glu Gln Asp Lys Phe Ser Gln Ala Ala Lys Val | | |
| 275 | 280 | 285 |
| Ala Glu Leu Glu Lys Arg Leu Thr Glu Leu Glu Thr Ala Val Arg Cys | | |
| 290 | 295 | 300 |
| Asp Gln Asp Ala Gln Asn Pro Leu Ser Ala Gly Leu Gln Gly Ala Cys | | |
| 305 | 310 | 320 |
| Leu Met Glu Thr Val Glu Leu Leu Gln Ala Lys Val Ser Ala Leu Asp | | |
| 325 | 330 | 335 |
| Leu Ala Val Leu Asp Gln Val Glu Ala Arg Leu Gln Ser Val Leu Gly | | |
| 340 | 345 | 350 |
| Lys Val Asn Glu Ile Ala Lys His Lys Ala Ser Val Glu Asp Ala Asp | | |
| 355 | 360 | 365 |
| Thr Gln Ser Lys Val His Gln Leu Tyr Glu Thr Ile Gln Arg Trp Ser | | |
| 370 | 375 | 380 |
| Pro Ile Ala Ser Thr Leu Pro Glu Leu Val Gln Arg Leu Val Thr Ile | | |
| 385 | 390 | 400 |
| Lys Gln Leu His Glu Gln Ala Met Gln Phe Gly Gln Leu Leu Thr His | | |
| 405 | 410 | 415 |
| Leu Asp Thr Thr Gln Gln Met Ile Ala Asn Ser Leu Lys Asp Asn Thr | | |
| 420 | 425 | 430 |
| Thr Leu Leu Thr Gln Val Gln Thr Thr Met Arg Glu Asn Leu Ala Thr | | |

648

435 440 445
Val Glu Gly Asn Phe Ala Ser Ile Asp Glu Arg Met Lys Lys Leu Gly
450 455 460

Lys
465

<210> 677
<211> 48
<212> PRT
<213> Homo sapiens

<400> 677
Ser Ser Phe Leu Asn Ser Asp Leu Gly Leu Ser Leu Ala Arg Asn Leu
1 5 10 15
Ala Phe Ser Phe Thr Thr Lys Glu Arg Asp Gln Lys Pro Leu Ile Phe
20 25 30
Asn Phe His Lys Met Leu Glu Val Tyr Ile Tyr Ile Tyr Ile Phe Leu
35 40 45

<210> 678
<211> 940
<212> PRT
<213> Homo sapiens

<400> 678
Val Leu Gly Glu Gly Ile Ser Phe Leu Leu Ser Pro Pro Leu Pro Thr
1 5 10 15
Pro Ser Ile Asn Ile Ile Leu Leu Lys Ile Leu Arg Cys Gln Ala Ala
20 25 30
Lys Val Glu Ser Ala Ile Ala Glu Gly Gly Ala Ser Arg Phe Ser Ala
35 40 45
Ser Ser Gly Gly Gly Gly Ser Arg Gly Ala Pro Gln His Tyr Pro Lys
50 55 60
Thr Ala Gly Asn Ser Glu Phe Leu Gly Lys Thr Pro Gly Gln Asn Ala
65 70 75 80

649

Gln Lys Trp Ile Pro Ala Arg Ser Thr Arg Arg Asp Asp Asn Ser Ala
 85 90 95
 Ala Asn Asn Ser Ala Asn Glu Lys Glu Arg His Asp Ala Ile Phe Arg
 100 105 110
 Lys Val Arg Gly Ile Leu Asn Lys Leu Thr Pro Glu Lys Phe Asp Lys
 115 120 125
 Leu Cys Leu Glu Leu Leu Asn Val Gly Val Glu Ser Lys Leu Ile Leu
 130 135 140
 Lys Gly Val Ile Leu Leu Ile Val Asp Lys Ala Leu Glu Glu Pro Lys
 145 150 155 160
 Tyr Ser Ser Leu Tyr Ala Gln Leu Cys Leu Arg Leu Ala Glu Asp Ala
 165 170 175
 Pro Asn Phe Asp Gly Pro Ala Ala Glu Gly Gln Pro Gly Gln Lys Gln
 180 185 190
 Ser Thr Thr Phe Arg Arg Leu Leu Ile Ser Lys Leu Gln Asp Glu Phe
 195 200 205
 Glu Asn Arg Thr Arg Asn Val Asp Val Tyr Asp Lys Arg Glu Asn Pro
 210 215 220
 Leu Leu Pro Glu Glu Glu Glu Gln Arg Ala Ile Ala Lys Ile Lys Met
 225 230 235 240
 Leu Gly Asn Ile Lys Phe Ile Gly Glu Leu Gly Lys Leu Asp Leu Ile
 245 250 255
 His Glu Ser Ile Leu His Lys Cys Ile Lys Thr Leu Leu Glu Lys Lys
 260 265 270
 Lys Arg Val Gln Leu Lys Asp Met Gly Glu Asp Leu Glu Cys Leu Cys
 275 280 285
 Gln Ile Met Arg Thr Val Gly Pro Arg Leu Asp His Glu Arg Ala Lys
 290 295 300
 Ser Leu Met Asp Gln Tyr Phe Ala Arg Met Cys Ser Leu Met Leu Ser
 305 310 315 320
 Lys Glu Leu Pro Ala Arg Ile Arg Phe Leu Leu Gln Asp Thr Val Glu
 325 330 335
 Leu Arg Glu His His Trp Val Pro Arg Lys Ala Phe Leu Asp Asn Gly
 340 345 350

650

Pro Lys Thr Ile Asn Gln Ile Arg Gln Asp Ala Val Lys Asp Leu Gly
 355 360 365
 Val Phe Ile Pro Ala Pro Met Ala Gln Gly Met Arg Ser Asp Phe Phe
 370 375 380
 Leu Glu Gly Pro Phe Met Pro Pro Arg Met Lys Met Asp Arg Asp Pro
 385 390 395 400
 Leu Gly Gly Leu Ala Asp Met Phe Gly Gln Met Pro Gly Ser Gly Ile
 405 410 415
 Gly Thr Gly Pro Gly Val Ile Gln Asp Arg Phe Ser Pro Thr Met Gly
 420 425 430
 Arg His Arg Ser Asn Gln Leu Phe Asn Gly His Gly Gly His Ile Met
 435 440 445
 Pro Pro Thr Gln Ser Gln Phe Gly Glu Met Gly Gly Lys Phe Met Lys
 450 455 460
 Ser Gln Gly Leu Ser Gln Leu Tyr His Asn Gln Ser Gln Gly Leu Leu
 465 470 475 480
 Ser Gln Leu Gln Gly Gln Ser Lys Asp Met Pro Pro Arg Phe Ser Lys
 485 490 495
 Lys Gly Gln Leu Asn Ala Asp Glu Ile Ser Leu Arg Pro Ala Gln Ser
 500 505 510
 Phe Leu Met Asn Lys Asn Gln Val Pro Lys Leu Gln Pro Gln Ile Thr
 515 520 525
 Met Ile Pro Pro Ser Ala Gln Pro Pro Arg Thr Gln Thr Pro Pro Leu
 530 535 540
 Gly Gln Thr Pro Gln Leu Gly Leu Lys Thr Asn Pro Pro Leu Ile Gln
 545 550 555 560
 Glu Lys Pro Ala Lys Thr Ser Lys Lys Pro Pro Pro Ser Lys Glu Glu
 565 570 575
 Leu Leu Lys Leu Thr Glu Thr Val Val Thr Glu Tyr Leu Asn Ser Gly
 580 585 590
 Asn Ala Asn Glu Ala Val Asn Gly Val Arg Glu Met Arg Ala Pro Lys
 595 600 605
 His Phe Leu Pro Glu Met Leu Ser Lys Val Ile Ile Leu Ser Leu Asp
 610 615 620

651

Arg Ser Asp Glu Asp Lys Glu Lys Ala Ser Ser Leu Ile Ser Leu Leu
 625 630 635 640

Lys Gln Glu Gly Ile Ala Thr Ser Asp Asn Phe Met Gln Ala Phe Leu
 645 650 655

Asn Val Leu Asp Gln Cys Pro Lys Leu Glu Val Asp Ile Pro Leu Val
 660 665 670

Lys Ser Tyr Leu Ala Gln Phe Ala Ala Arg Ala Ile Ile Ser Glu Leu
 675 680 685

Val Ser Ile Ser Glu Leu Ala Gln Pro Leu Glu Ser Gly Thr His Phe
 690 695 700

Pro Leu Phe Leu Leu Cys Leu Gln Gln Leu Ala Lys Leu Gln Asp Arg
 705 710 715 720

Glu Trp Leu Thr Glu Leu Phe Gln Gln Ser Lys Val Asn Met Gln Lys
 725 730 735

Met Leu Pro Glu Ile Asp Gln Asn Lys Asp Arg Met Leu Glu Ile Leu
 740 745 750

Glu Gly Lys Gly Leu Ser Phe Leu Phe Pro Leu Leu Lys Leu Glu Lys
 755 760 765

Glu Leu Leu Lys Gln Ile Lys Leu Asp Pro Ser Pro Gln Thr Ile Tyr
 770 775 780

Lys Trp Ile Lys Asp Asn Ile Ser Pro Lys Leu His Val Asp Lys Gly
 785 790 795 800

Phe Val Asn Ile Leu Met Thr Ser Phe Leu Gln Tyr Ile Ser Ser Glu
 805 810 815

Val Asn Pro Pro Ser Asp Glu Thr Asp Ser Ser Ser Ala Pro Ser Lys
 820 825 830

Glu Gln Leu Glu Gln Glu Lys Gln Leu Leu Leu Ser Phe Lys Pro Val
 835 840 845

Met Gln Lys Phe Leu His Asp His Val Asp Leu Gln Val Ser Ala Leu
 850 855 860

Tyr Ala Leu Gln Val His Cys Tyr Asn Ser Asn Phe Pro Lys Gly Met
 865 870 875 880

Leu Leu Arg Phe Phe Val His Phe Tyr Asp Met Glu Ile Ile Glu Glu
 885 890 895

652

Glu Ala Phe Leu Ala Trp Lys Glu Asp Ile Thr Gln Glu Phe Pro Gly
 900 905 910

Lys Gly Lys Ala Leu Phe Gln Val Asn Gln Trp Leu Thr Trp Leu Gln
 915 920 925

Thr Ala Glu Glu Glu Glu Ser Glu Glu Glu Ala Asp
 930 935 940

<210> 679

<211> 212

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (7)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (160)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (172)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 679

Ser Trp Lys Glu Glu Glu Xaa Lys Pro His Leu Gln Gly Lys Pro Gly
 1 5 10 15

Arg Pro Leu Ser Pro Ala Asn Val Pro Ala Leu Pro Gly Glu Thr Val
 20 25 30

Thr Ser Pro Val Arg Leu His Pro Asp Tyr Leu Ser Pro Glu Glu Ile
 35 40 45

Gln Arg Gln Leu Gln Asp Ile Glu Arg Arg Leu Asp Ala Leu Glu Leu
 50 55 60

Arg Gly Val Glu Leu Glu Lys Arg Leu Arg Ala Ala Glu Gly Asp Asp
 65 70 75 80

Ala Glu Asp Ser Leu Met Val Asp Trp Phe Trp Leu Ile His Glu Lys
 85 90 95

Gln Leu Leu Leu Arg Gln Glu Ser Glu Leu Met Tyr Lys Ser Lys Ala

653

| 100 | 105 | 110 |
|---|-----|---------|
| Gln Arg Leu Glu Glu Gln Gln Leu Asp Ile Glu Gly Glu Leu Arg Arg | | |
| 115 | 120 | 125 |
| Leu Met Ala Lys Pro Glu Ala Leu Lys Ser Leu Gln Glu Arg Arg Arg | | |
| 130 | 135 | 140 |
| Glu Gln Glu Leu Leu Glu Gln Tyr Val Ser Thr Val Asn Asp Arg Xaa | | |
| 145 | 150 | 155 160 |
| Asp Ile Val Asp Ser Leu Asp Glu Asp Arg Leu Xaa Glu Gln Glu Glu | | |
| 165 | 170 | 175 |
| Asp Gln Met Leu Arg Asp Met Ile Glu Lys Leu Gly Leu Gln Arg Lys | | |
| 180 | 185 | 190 |
| Lys Ser Lys Phe Arg Leu Ser Lys Ile Trp Ser Pro Lys Ser Lys Ser | | |
| 195 | 200 | 205 |
| Ser Pro Ser Gln | | |
| 210 | | |

<210> 680
 <211> 412
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (172)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (404)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 680
 Val Ala Val Glu Leu Gly Ser Leu Arg Gly Gly Thr Met Ala Ser Glu
 1 5 10 15
 Lys Pro Leu Ala Val Thr Cys Thr Ala Pro Val Asn Ile Ala Val
 20 25 30
 Ile Lys Tyr Trp Gly Lys Arg Asp Glu Glu Leu Val Leu Pro Ile Asn
 35 40 45
 Ser Ser Leu Ser Val Thr Leu His Gln Asp Gln Leu Lys Thr Thr Thr

654

50 55 60

Thr Ala Val Ile Ser Lys Asp Phe Thr Glu Asp Arg Ile Trp Leu Asn
65 70 75 80

Gly Arg Glu Glu Asp Val Gly Gln Pro Arg Leu Gln Ala Cys Leu Arg
85 90 95

Glu Ile Arg Cys Leu Ala Arg Lys Arg Arg Asn Ser Arg Asp Gly Asp
100 105 110

Pro Leu Pro Ser Ser Leu Ser Cys Lys Val His Val Ala Ser Val Asn
115 120 125

Asn Phe Pro Thr Ala Ala Gly Leu Ala Ser Ser Ala Ala Gly Tyr Ala
130 135 140

Cys Leu Ala Tyr Thr Leu Ala Arg Val Tyr Gly Val Glu Ser Asp Leu
145 150 155 160

Ser Glu Val Ala Arg Arg Gly Ser Gly Ser Ala Xaa Arg Ser Leu Tyr
165 170 175

Gly Gly Phe Val Glu Trp Gln Met Gly Glu Gln Ala Asp Gly Lys Asp
180 185 190

Ser Ile Ala Arg Gln Val Ala Pro Glu Ser His Trp Pro Glu Leu Arg
195 200 205

Val Leu Ile Leu Val Val Ser Ala Glu Lys Lys Leu Thr Gly Ser Thr
210 215 220

Val Gly Met Arg Ala Ser Val Glu Thr Ser Pro Leu Leu Arg Phe Arg
225 230 235 240

Ala Glu Ser Val Val Pro Ala Arg Met Ala Glu Met Ala Arg Cys Ile
245 250 255

Arg Glu Arg Asp Phe Pro Ser Phe Ala Gln Leu Thr Met Lys Asp Ser
260 265 270

Asn Gln Phe His Ala Thr Cys Leu Asp Thr Phe Pro Pro Ile Ser Tyr
275 280 285

Leu Asn Ala Ile Ser Trp Arg Ile Ile His Leu Val His Arg Phe Asn
290 295 300

Ala His His Gly Asp Thr Lys Val Ala Tyr Thr Phe Asp Ala Gly Pro
305 310 315 320

Asn Ala Val Ile Phe Thr Leu Asp Asp Thr Val Ala Glu Phe Val Ala

325 330 335

Leu Leu Gly Xaa Asp Gly Leu Pro Lys Pro Ala Ala
405 410

Pro Arg Glu Arg Asn Cys Ala Pro Ser Val Leu Leu Pro
50 55 60

Gln Arg Pro Pro Pro Gln Ser Pro Thr Ala Thr Gly Leu Gly Pro Ala
20 25 30

656

Ala Arg Ser Cys Leu Pro Gln Pro Pro Ser Arg Gly Pro Gln Pro Pro
 35 40 45
 Pro Thr Leu Pro His Gly Pro Gly Ala Met Ser Glu Leu Glu Gln Leu
 50 55 60
 Arg Gln Glu Ala Glu Gln Leu Arg Asn Gln Ile Arg Asp Ala Arg Lys
 65 70 75 80
 Ala Cys Gly Asp Ser Thr Leu Thr Gln Ile Thr Ala Gly Leu Asp Pro
 85 90 95
 Val Gly Arg Ile Gln Met Arg Thr Arg Arg Thr Leu Arg Gly His Leu
 100 105 110
 Ala Lys Ile Tyr Ala Met His Trp Gly Thr Asp Ser Arg Leu Leu Val
 115 120 125
 Ser Ala Ser Gln Asp Gly Lys Leu Ile Ile Trp Asp Ser Tyr Thr Thr
 130 135 140
 Asn Lys Val His Ala Ile Pro Leu Arg Ser Ser Trp Val Met Thr Cys
 145 150 155 160
 Ala Tyr Ala Pro Ser Gly Asn Phe Val Ala Cys Gly Gly Leu Asp Asn
 165 170 175
 Ile Cys Ser Ile Tyr Ser Leu Lys Thr Arg Glu Ala Thr Ser Gly Ser
 180 185 190
 Ala Gly Ser Cys Leu Ala Thr Leu Gly Thr Cys Arg Val Ala Ala Ser
 195 200 205
 Trp Met Thr Thr Lys Ser Ser Pro Ala Leu Gly Ile Pro Pro Val Pro
 210 215 220
 Cys Gly Thr Leu Arg Gln Ala Ser Arg Gln Trp Val Leu Leu Asp Thr
 225 230 235 240
 Val Gly Met

<210> 683
 <211> 146
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE

657

<222> (133)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 683

Asp Leu Glu Gly Asp Ala Gly Tyr Thr Gly Gly Leu Arg Gln Gly His
 1 5 10 15

Ala Gly Gly Ala Gly Glu Leu Ala Arg Thr Leu Ala Leu Lys Pro Thr
 20 25 30

Ser Leu Glu Leu Phe Arg Thr Lys Val Asn Ala Leu Thr Tyr Gly Glu
 35 40 45

Val Leu Arg Leu Arg Gln Thr Glu Arg Leu His Gln Glu Gly Thr Leu
 50 55 60

Ala Pro Pro Ile Leu Glu Leu Arg Glu Lys Leu Lys Pro Glu Leu Met
 65 70 75 80

Gly Leu Ile Arg Gln Gln Arg Leu Leu Arg Leu Cys Glu Gly Thr Leu
 85 90 95

Phe Arg Lys Ile Ser Ser Arg Arg Arg Gln Asp Lys Leu Trp Phe Cys
 100 105 110

Cys Leu Ser Pro Asn His Lys Leu Leu Gln Tyr Gly Asp Met Glu Glu
 115 120 125

Gly Ala Ser Ala Xaa Pro Trp Arg Val Cys Pro Ser Asn Ser Leu Trp
 130 135 140

Pro Thr
 145

<210> 684

<211> 300

<212> PRT

<213> Homo sapiens

<400> 684

Val Tyr Ser Cys Gly Phe Gln Val Gln Ser Trp Ser Pro Arg Trp Ile
 1 5 10 15

Trp Val Thr Thr Lys Ser Lys Ile Gly Ala Pro Arg Ser Ser Phe Cys
 20 25 30

Trp His Arg Leu Pro Ser Thr Ser Gln Leu His Leu Cys Pro Ala Glu
 35 40 45

658

Gly Glu Ala Pro Ser Ala Gly Glu Ala Ala Pro Arg Ala Pro Thr Gly
50 55 60

Ser Glu Pro Lys Pro Gly Ala Leu Pro Trp Gly Pro Arg Ala Pro Asp
65 70 75 80

Ser Glu Gly Gly Gly Gly Ala Gly Ala Ala Asp Pro Ala Ala Asn Ala
85 90 95

Gly His Gly Ala Ser Ser Glu Ala Glu Cys Gly Cys Gln Arg Thr Leu
100 105 110

Arg Pro Met Pro Ser Thr Pro Gly Pro Gly Ala Ala Ala Val Arg Ala
115 120 125

Leu Gly Gln Leu Phe His Ile Ala Cys Phe Thr Cys His Gln Cys Ala
130 135 140

Gln Gln Leu Gln Gly Gln Gln Phe Tyr Ser Leu Glu Gly Ala Pro Tyr
145 150 155 160

Cys Glu Gly Cys Tyr Thr Asp Thr Leu Glu Lys Cys Asn Thr Cys Gly
165 170 175

Glu Pro Ile Thr Asp Arg Met Leu Arg Ala Thr Gly Lys Ala Tyr His
180 185 190

Pro His Cys Phe Thr Cys Val Val Cys Ala Arg Pro Leu Glu Gly Thr
195 200 205

Ser Phe Ile Val Asp Gln Ala Asn Arg Pro His Cys Val Pro Asp Tyr
210 215 220

His Lys Gln Tyr Ala Pro Arg Cys Ser Val Cys Ser Glu Pro Ile Met
225 230 235 240

Pro Glu Pro Gly Arg Asp Glu Thr Val Arg Val Val Ala Leu Asp Lys
245 250 255

Asn Phe His Met Lys Cys Tyr Lys Cys Glu Asp Cys Gly Lys Pro Leu
260 265 270

Ser Ile Glu Ala Asp Asp Asn Gly Cys Phe Pro Leu Asp Gly His Val
275 280 285

Leu Cys Arg Lys Cys His Thr Ala Arg Ala Gln Thr
290 295 300

<210> 685

659

<211> 130

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (61)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 685

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Arg | His | Glu | Asp | Cys | Pro | Thr | Pro | Ser | Gln | Cys | Val | Val | Ala | Arg |
| 1 | | | | 5 | | | | 10 | | | | | 15 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Leu | Gly | Lys | Gln | Gln | Thr | Val | Met | Ala | Ile | Ala | Thr | Lys | Ile | Ala |
| | | 20 | | | | | | 25 | | | | | 30 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Leu | Gln | Met | Asn | Cys | Lys | Met | Gly | Gly | Glu | Leu | Trp | Arg | Val | Asp | Ile |
| | | 35 | | | | | 40 | | | | | 45 | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Leu | Lys | Leu | Val | Met | Ile | Val | Gly | Ile | Asp | Cys | Xaa | His | Asp | Met |
| | 50 | | | | | 55 | | | | | 60 | | | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Thr | Ala | Gly | Arg | Arg | Ser | Ile | Ala | Gly | Phe | Val | Ala | Ser | Ile | Asn | Glu |
| 65 | | | | | 70 | | | | 75 | | | | | 80 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Gly | Met | Thr | Arg | Trp | Phe | Ser | Arg | Cys | Ile | Phe | Gln | Asp | Arg | Gly | Gln |
| | | | 85 | | | | | | 90 | | | | | 95 | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Glu | Leu | Val | Asp | Gly | Leu | Lys | Val | Cys | Leu | Gln | Ala | Ala | Leu | Arg | Ala |
| | | 100 | | | | | | 105 | | | | | 110 | | |

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Trp | Asn | Ser | Cys | Asn | Glu | Tyr | Met | Pro | Ser | Arg | Ile | Ile | Val | Tyr | Arg |
| | 115 | | | | | | 120 | | | | | 125 | | | |

| | |
|-----|-----|
| Val | Ala |
| | 130 |

<210> 686

<211> 207

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (84)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 686

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Ile | Tyr | Gln | Val | Tyr | Asn | Ala | Leu | Gln | Glu | Lys | Val | Gln | Ala | Val | Cys |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|

660

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      1           5           10           15
Ala Asp Val Glu Lys Ser Glu Arg Val Val Glu Ser Cys Gln Ala Glu
      20           25           30
Val Asn Lys Leu Arg Arg Gln Ile Thr Gln Arg Lys Asn Glu Lys Glu
      35           40           45
Gln Glu Arg Arg Leu Gln Gln Ala Val Leu Ser Arg Gln Met Pro Ser
      50           55           60
Glu Ser Leu Asp Pro Ala Phe Ser Pro Arg Met Pro Ser Ser Gly Phe
      65           70           75           80
Ala Ala Glu Xaa Arg Ser Thr Leu Gly Asp Ala Glu Ala Ser Asp Pro
      85           90           95
Pro Pro Pro Tyr Ser Asp Phe His Pro Asn Asn Gln Glu Ser Thr Leu
      100          105          110
Ser His Ser Arg Met Glu Arg Ser Val Phe Met Pro Arg Pro Gln Ala
      115          120          125
Val Gly Ser Ser Asn Tyr Ala Ser Thr Ser Ala Gly Leu Lys Tyr Pro
      130          135          140
Gly Ser Gly Ala Asp Leu Pro Pro Pro Gln Arg Ala Ala Gly Asp Ser
      145          150          155          160
Gly Glu Asp Ser Asp Asp Ser Asp Tyr Glu Asn Leu Ile Asp Pro Thr
      165          170          175
Glu Pro Ser Asn Ser Glu Tyr Ser His Ser Lys Asp Ser Arg Pro Met
      180          185          190
Ala His Pro Asp Glu Asp Pro Arg Asn Thr Gln Thr Ser Gln Ile
      195          200          205

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<210> 687

<211> 101

<212> PRT

<213> Homo sapiens

<400> 687

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Ala Arg Ala Gly Glu Gly Val Val Thr Arg Trp Arg His Arg Leu
  1           5           10           15
Gly Gln Gly Ala Cys Pro Trp Asp Arg Ser Arg Pro Met Glu Pro Pro
      20           25           30

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661

Gly Arg Ser Ser Arg Ser Thr Ala Ser His Thr Leu His Gln Tyr Cys
35 40 45
Cys Pro Thr Gln Val Leu Asp Ser Met Lys Leu Thr Pro Ser Gly Arg
50 55 60
Leu Ala Glu Ser Arg Glu Glu Glu Glu Glu Thr Glu Glu Glu
65 70 75 80
Glu Glu Glu Asp Ala His Gln Phe Cys Cys Pro Ala Ser Glu Cys Ser
85 90 95
Ser Pro Ser Ser Arg
100

<210> 688
<211> 62
<212> PRT
<213> Homo sapiens

<400> 688
Glu Arg Asn Ala Asp Pro Pro Asp Val Ser Leu Gly Lys Ala Val Asn
1 5 10 15
Gln Leu Ile Phe Ile Glu Asp Leu Leu Cys Pro Leu His Arg Val Ala
20 25 30
Ser Val Arg Glu Ser Trp Phe Phe Pro Arg Asn Thr Asp Phe Leu Ser
35 40 45
Gly Arg Leu His Val Phe Ile Tyr Phe His His Ser Arg Phe
50 55 60

<210> 689
<211> 549
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (1)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (7)

662

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 689

Xaa Arg Trp Ala Cys Gly Xaa Leu Leu Leu Leu Val Arg Gly Gln Gly
1 5 10 15

Gln Asp Ser Ala Ser Pro Ile Arg Thr Thr His Thr Gly Gln Val Leu
20 25 30

Gly Ser Leu Val His Val Lys Gly Ala Asn Ala Gly Val Gln Thr Phe
35 40 45

Leu Gly Ile Pro Phe Ala Lys Pro Pro Leu Gly Pro Leu Arg Phe Ala
50 55 60

Pro Pro Glu Pro Pro Glu Ser Trp Ser Gly Val Arg Asp Gly Thr Thr
65 70 75 80

His Pro Ala Met Cys Leu Gln Asp Leu Thr Ala Val Glu Ser Glu Phe
85 90 95

Leu Ser Gln Phe Asn Met Thr Phe Pro Ser Asp Ser Met Ser Glu Asp
100 105 110

Cys Leu Tyr Leu Ser Ile Tyr Thr Pro Ala His Ser His Glu Gly Ser
115 120 125

Asn Leu Pro Val Met Val Trp Ile His Gly Gly Ala Leu Val Phe Gly
130 135 140

Met Ala Ser Leu Tyr Asp Gly Ser Met Leu Ala Ala Leu Glu Asn Val
145 150 155 160

Val Val Val Ile Ile Gln Tyr Arg Leu Gly Val Leu Gly Phe Phe Ser
165 170 175

Thr Gly Asp Lys His Ala Thr Gly Asn Trp Gly Tyr Leu Asp Gln Val
180 185 190

Ala Ala Leu Arg Trp Val Gln Gln Asn Ile Ala His Phe Gly Gly Asn
195 200 205

Pro Asp Arg Val Thr Ile Phe Gly Glu Ser Ala Gly Gly Thr Ser Val
210 215 220

Ser Ser Leu Val Val Ser Pro Ile Ser Gln Gly Leu Phe His Gly Ala
225 230 235 240

Ile Met Glu Ser Gly Val Ala Leu Leu Pro Gly Leu Ile Ala Ser Ser
245 250 255

Ala Asp Val Ile Ser Thr Val Val Ala Asn Leu Ser Ala Cys Asp Gln
 260 265 270
 Val Asp Ser Glu Ala Leu Val Gly Cys Leu Arg Gly Lys Ser Lys Glu
 275 280 285
 Glu Ile Leu Ala Ile Asn Lys Pro Phe Lys Met Ile Pro Gly Val Val
 290 295 300
 Asp Gly Val Phe Leu Pro Arg His Pro Gln Glu Leu Leu Ala Ser Ala
 305 310 315 320
 Asp Phe Gln Pro Val Pro Ser Ile Val Gly Val Asn Asn Asn Glu Phe
 325 330 335
 Gly Trp Leu Ile Pro Lys Val Met Arg Ile Tyr Asp Thr Gln Lys Glu
 340 345 350
 Met Asp Arg Glu Ala Ser Gln Ala Ala Leu Gln Lys Met Leu Thr Leu
 355 360 365
 Leu Met Leu Pro Pro Thr Phe Gly Asp Leu Leu Arg Glu Glu Tyr Ile
 370 375 380
 Gly Asp Asn Gly Asp Pro Gln Thr Leu Gln Ala Gln Phe Gln Glu Met
 385 390 395 400
 Met Ala Asp Ser Met Phe Val Ile Pro Ala Leu Gln Val Ala His Phe
 405 410 415
 Gln Cys Ser Arg Ala Pro Val Tyr Phe Tyr Glu Phe Gln His Gln Pro
 420 425 430
 Ser Trp Leu Lys Asn Ile Arg Pro Pro His Met Lys Ala Asp His Gly
 435 440 445
 Asp Glu Leu Pro Phe Val Phe Arg Ser Phe Phe Gly Gly Asn Tyr Ile
 450 455 460
 Lys Phe Thr Glu Glu Glu Glu Gln Leu Ser Arg Lys Met Met Lys Tyr
 465 470 475 480
 Trp Ala Asn Phe Ala Arg Asn Gly Asn Pro Asn Gly Glu Gly Leu Pro
 485 490 495
 His Trp Pro Leu Phe Asp Gln Glu Glu Gln Tyr Leu Gln Leu Asn Leu
 500 505 510
 Gln Pro Ala Val Gly Arg Ala Leu Lys Ala His Arg Leu Gln Phe Trp
 515 520 525

664

Lys Lys Ala Leu Pro Gln Lys Ile Gln Glu Leu Glu Glu Pro Glu Glu
 530 535 540

Arg His Thr Glu Leu
 545

<210> 690

<211> 155

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (36)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (46)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (50)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (85)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 690

Ser His Arg Val Thr His Cys Pro Tyr Ala Val Ala Leu Pro Glu Val
 1 5 10 15

Ala Pro Ala Gln Pro Leu Thr Glu Ala Leu Arg Ala Leu Cys His Val
 20 25 30

Gly Leu Phe Xaa Phe Ala Phe Cys Ala Leu Phe Asp Cys Xaa Arg Pro
 35 40 45

Val Xaa Gln Lys Ser Cys Asp Leu Leu Leu Phe Leu Arg Asp Lys Ile
 50 55 60

Ala Ser Tyr Ser Ser Leu Arg Glu Ala Arg Gly Ser Pro Asn Thr Ala
 65 70 75 80

Ser Ala Glu Ala Xaa Leu Pro Arg Trp Arg Ala Gly Glu Gln Ala Gln
 85 90 95

665

Pro Pro Gly Asp Gln Glu Pro Glu Ala Val Leu Ala Met Leu Arg Ser
 100 105 110

Leu Asp Leu Glu Gly Leu Arg Ser Thr Leu Ala Glu Ser Ser Asp His
 115 120 125

Val Glu Lys Ser Pro Gln Ser Leu Leu Gln Asp Met Leu Ala Thr Gly
 130 135 140

Gly Phe Leu Gln Gly Asp Glu Ala Asp Cys Tyr
 145 150 155

<210> 691

<211> 149

<212> PRT

<213> Homo sapiens

<400> 691

Met Cys Leu Glu Arg Pro Leu Arg Glu Gly Pro Arg Val Met Glu Lys
 1 5 10 15

Glu Ala Trp Pro Gly Ser Leu Glu Gly Arg Gly Gly Gly Trp Arg His
 20 25 30

Leu Asp Cys Pro Leu Leu Ser His Thr Trp Gly Val Val Thr Pro Phe
 35 40 45

Thr Pro Ala Arg Leu Pro Ser Ala Phe His Glu Leu His Leu Leu Pro
 50 55 60

Thr Ser Leu Trp Arg Gly Trp Gly Pro Leu Ala Ser Thr Arg Gly Pro
 65 70 75 80

Ser Ala Ser Pro Lys Pro Glu Pro Ser Ala Pro Gly Glu Asn Lys Trp
 85 90 95

Leu Ser Phe Asp Thr Trp Gly Arg Arg Glu Ala Ala Gly Trp Arg Gln
 100 105 110

Ser Gln Gly Arg Asp Thr Thr Glu Gly Asp Pro Asp Ile Pro Arg Lys
 115 120 125

Phe Pro Ala Glu Gln Thr Ala Phe Gln Pro Glu Ala Cys Leu Asn Cys
 130 135 140

Val Met Cys Asn Asn
 145

666

<210> 692
 <211> 218
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (160)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 692

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Pro | Gly | Val | Lys | Leu | Trp | Asp | Val | Pro | Val | Met | Leu | Asp | His | Lys | Asp |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Leu | Glu | Ala | Glu | Ile | His | Pro | Leu | Lys | Asn | Glu | Glu | Arg | Lys | Ser | Gln |
| | | | 20 | | | | | 25 | | | | | 30 | | |
| Glu | Asn | Leu | Gly | Asn | Pro | Ser | Lys | Asn | Glu | Asp | Asn | Val | Lys | Ser | Ala |
| | 35 | | | | | | 40 | | | | | 45 | | | |
| Pro | Pro | Gln | Ser | Arg | Leu | Ser | Arg | Cys | Arg | Ala | Ala | Ala | Phe | Phe | Leu |
| | 50 | | | | | 55 | | | | | 60 | | | | |
| Ser | Leu | Phe | Leu | Cys | Leu | Phe | Val | Val | Phe | Val | Val | Ser | Phe | Val | Ile |
| 65 | | | | | 70 | | | | 75 | | | | | | 80 |
| Pro | Cys | Pro | Asp | Arg | Pro | Ala | Ser | Gln | Arg | Met | Trp | Arg | Ile | Asp | Tyr |
| | | | | 85 | | | | | 90 | | | | | 95 | |
| Ser | Ala | Ala | Val | Ile | Tyr | Asp | Phe | Leu | Ala | Val | Asp | Asp | Ile | Asn | Gly |
| | | | 100 | | | | | 105 | | | | | 110 | | |
| Asp | Arg | Ile | Gln | Asp | Val | Leu | Phe | Leu | Tyr | Lys | Asn | Thr | Asn | Ser | Ser |
| | 115 | | | | | | 120 | | | | | 125 | | | |
| Asn | Asn | Phe | Ser | Arg | Ser | Cys | Val | Asp | Glu | Gly | Phe | Ser | Ser | Pro | Cys |
| | 130 | | | | | 135 | | | | | 140 | | | | |
| Thr | Phe | Ala | Ala | Ala | Val | Ser | Gly | Ala | Asn | Ala | Ala | Arg | Ser | Gly | Xaa |
| 145 | | | | | 150 | | | | | 155 | | | | 160 | |
| Asp | Leu | Trp | Pro | Lys | Thr | Trp | Pro | Ser | Trp | Ser | Val | Leu | Cys | Pro | Ser |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Gln | Glu | Ala | Val | Arg | His | Leu | Leu | Pro | Ala | Ser | Trp | Trp | Ala | Asp | Pro |
| | | | 180 | | | | | 185 | | | | | 190 | | |
| Val | Leu | Ser | Leu | Gln | Ser | Thr | Cys | Ser | Gln | Gly | Lys | Pro | Trp | Lys | Pro |
| | 195 | | | | | | 200 | | | | | 205 | | | |

Gln Pro Ala Val Gln Gly Glu Trp Ser Ile
210 215

<210> 693
<211> 68
<212> PRT
<213> Homo sapiens

<400> 693
Ser Cys Asn Ser Ser Asn Asn Ile Leu Gln Leu Pro Tyr Arg Asn Arg
1 5 10 15
Ser Gly Arg Ala Lys Ser Asp Leu Gly Lys Val Ile Arg Tyr Arg Leu
20 25 30
Ser Ile Pro Phe Pro Lys Met Leu Gly Thr Arg Ser Ile Ser Asp Phe
35 40 45
Ile Ile Phe Phe Lys Val Trp Asn Ile Cys Ile Ile Leu Thr Ser Trp
50 55 60
Ala Ser Gln Ile
65

<210> 694
<211> 234
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (3)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (4)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (219)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 694
Cys Ala Xaa Xaa Leu Arg Gly Phe Asp Gln Gln Met Ser Ser Met Val

668

1 5 10 15
Ile Glu His Met Ala Ser His Gly Thr Arg Phe Leu Arg Gly Cys Ala
20 25 30
Pro Ser Arg Val Arg Arg Leu Pro Asp Gly Gln Leu Gln Val Thr Trp
35 40 45
Glu Asp Ser Thr Thr Gly Lys Glu Asp Thr Gly Thr Phe Asp Thr Val
50 55 60
Leu Trp Ala Ile Gly Arg Val Pro Asp Thr Arg Ser Leu Asn Leu Glu
65 70 75 80
Lys Ala Gly Val Asp Thr Ser Pro Asp Thr Gln Lys Ile Leu Val Asp
85 90 95
Ser Arg Glu Ala Thr Ser Val Pro His Ile Tyr Ala Ile Gly Asp Val
100 105 110
Val Glu Gly Arg Pro Glu Leu Thr Pro Thr Ala Ile Met Ala Gly Arg
115 120 125
Leu Leu Val Gln Arg Leu Phe Gly Gly Ser Ser Asp Leu Met Asp Tyr
130 135 140
Asp Asn Val Pro Thr Thr Val Phe Thr Pro Leu Glu Tyr Gly Cys Val
145 150 155 160
Gly Leu Ser Glu Glu Glu Ala Val Ala Arg His Gly Gln Glu His Val
165 170 175
Glu Val Tyr His Ala His Tyr Lys Pro Leu Glu Phe Thr Val Ala Gly
180 185 190
Arg Asp Ala Ser Gln Cys Tyr Val Lys Met Val Cys Leu Arg Glu Pro
195 200 205
Pro Gln Leu Val Leu Gly Leu His Phe Leu Xaa Pro Thr Gln Ala Asn
210 215 220
Tyr Ser Arg Ile Cys Ser Gly Asp Lys Cys
225 230

<210> 695

<211> 460

<212> PRT

<213> Homo sapiens

<400> 695

Pro Cys Pro Pro Arg Pro Gln Glu Leu Pro Gly Arg Ser Pro Ser Ser
1 5 10 15
Trp Ser Ala Leu Gly Trp Pro Ala Ala Leu Gly Gly Gly Val Val Ala
20 25 30
Val Ala Val Cys Glu Pro Val Ala Arg Leu Leu Trp Ala Gly Thr Leu
35 40 45
Lys Ile Ala Ala Met Ala Glu Asn Gly Asp Asn Glu Lys Met Ala Ala
50 55 60
Leu Glu Ala Lys Ile Cys His Gln Ile Glu Tyr Tyr Phe Gly Asp Phe
65 70 75 80
Asn Leu Pro Arg Asp Lys Phe Leu Lys Glu Gln Ile Lys Leu Asp Glu
85 90 95
Gly Trp Val Pro Leu Glu Ile Met Ile Lys Phe Asn Arg Leu Asn Arg
100 105 110
Leu Thr Thr Asp Phe Asn Val Ile Val Glu Ala Leu Ser Lys Ser Lys
115 120 125
Ala Glu Leu Met Glu Ile Ser Glu Asp Lys Thr Lys Ile Arg Arg Ser
130 135 140
Pro Ser Lys Pro Leu Pro Glu Val Thr Asp Glu Tyr Lys Asn Asp Val
145 150 155 160
Lys Asn Arg Ser Val Tyr Ile Lys Gly Phe Pro Thr Asp Ala Thr Leu
165 170 175
Asp Asp Ile Lys Glu Trp Leu Glu Asp Lys Gly Gln Val Leu Asn Ile
180 185 190
Gln Met Arg Arg Thr Leu His Lys Ala Phe Lys Gly Ser Ile Phe Val
195 200 205
Val Phe Asp Ser Ile Glu Ser Ala Lys Lys Phe Val Glu Thr Pro Gly
210 215 220
Gln Lys Tyr Lys Glu Thr Asp Leu Leu Ile Leu Phe Lys Asp Asp Tyr
225 230 235 240
Phe Ala Lys Lys Asn Glu Glu Arg Lys Gln Asn Lys Val Glu Ala Lys
245 250 255
Leu Arg Ala Lys Gln Glu Gln Glu Ala Lys Gln Lys Leu Glu Glu Asp
260 265 270

670

Ala Glu Met Lys Ser Leu Glu Glu Lys Ile Gly Cys Leu Leu Lys Phe
 275 280 285
 Ser Gly Asp Leu Asp Asp Gln Thr Cys Arg Glu Asp Leu His Ile Leu
 290 295 300
 Phe Ser Asn His Gly Glu Ile Lys Trp Ile Asp Phe Val Arg Gly Ala
 305 310 315 320
 Lys Glu Gly Ile Ile Leu Phe Lys Glu Lys Ala Lys Glu Ala Leu Gly
 325 330 335
 Lys Ala Lys Asp Ala Asn Asn Gly Asn Leu Gln Leu Arg Asn Lys Glu
 340 345 350
 Val Thr Trp Glu Val Leu Glu Gly Glu Val Glu Lys Glu Ala Leu Lys
 355 360 365
 Lys Ile Ile Glu Asp Gln Gln Glu Ser Leu Asn Lys Trp Lys Ser Lys
 370 375 380
 Gly Arg Arg Phe Lys Gly Lys Gly Lys Gly Asn Lys Ala Ala Gln Pro
 385 390 395 400
 Gly Ser Gly Lys Gly Lys Val Gln Phe Gln Gly Lys Lys Thr Lys Phe
 405 410 415
 Ala Ser Asp Asp Glu His Asp Glu His Asp Glu Asn Gly Ala Thr Gly
 420 425 430
 Pro Val Lys Arg Ala Arg Glu Glu Thr Asp Lys Glu Glu Pro Ala Ser
 435 440 445
 Lys Gln Gln Lys Thr Glu Asn Gly Ala Gly Asp Gln
 450 455 460

<210> 696

<211> 80

<212> PRT

<213> Homo sapiens

<400> 696

Gly Glu Glu Gly Val Gly Ser Pro Ser Gly Ile Leu Ala Thr Pro Leu
 1 5 10 15
 Arg Ser Ala Arg Gly Thr Thr His Thr His Thr His Thr His
 20 25 30

671

Thr His Ser His Thr His Ala His Phe Pro Ser Phe Pro Asp Pro Leu
 35 40 45
 Phe Gln Ser Ser Pro Phe Ser Ser Gly Phe Ile Asp Glu Tyr Lys Tyr
 50 55 60
 Pro His Leu Trp Pro Val Met Ser Val Thr Cys Cys Arg Phe Cys Val
 65 70 75 80

<210> 697

<211> 257

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (30)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 697

Trp Pro Arg Arg Pro Gly Pro His Leu Gly Val Leu Glu Phe Pro Gly
 1 5 10 15
 Ala Gly Cys Gly Ala Ser Ala Ala Gly Trp Pro Ser Ala Xaa Met Leu
 20 25 30
 Pro Gly Arg Gly Pro Arg Pro Phe Arg Ala Arg Leu Val Gly Arg Glu
 35 40 45
 Leu Val Ser Met Leu Ala Arg Glu Leu Pro Ala Ala Val Ala Pro Ala
 50 55 60
 Gly Pro Ala Ser Leu Ala Arg Trp Thr Leu Gly Phe Cys Asp Glu Arg
 65 70 75 80
 Leu Val Pro Phe Asp His Ala Glu Ser Thr Tyr Gly Leu Tyr Arg Thr
 85 90 95
 His Leu Leu Ser Arg Leu Pro Ile Pro Glu Ser Gln Val Ile Thr Ile
 100 105 110
 Asn Pro Glu Leu Pro Val Glu Glu Ala Ala Glu Asp Tyr Ala Lys Lys
 115 120 125
 Leu Arg Gln Ala Phe Gln Gly Asp Ser Ile Pro Val Phe Asp Leu Leu
 130 135 140

672

Ile Leu Gly Val Gly Pro Asp Gly His Thr Cys Ser Leu Phe Pro Asp
 145 150 155 160
 His Pro Leu Leu Gln Glu Arg Glu Lys Ile Val Ala Pro Ile Ser Asp
 165 170 175
 Ser Pro Lys Pro Pro Pro Gln Arg Val Thr Leu Thr Leu Pro Val Leu
 180 185 190
 Asn Ala Ala Arg Thr Val Ile Phe Val Ala Thr Gly Glu Gly Lys Ala
 195 200 205
 Ala Val Leu Lys Arg Ile Leu Glu Asp Gln Glu Glu Asn Pro Leu Pro
 210 215 220
 Ala Ala Leu Val Gln Pro His Thr Gly Lys Leu Cys Trp Phe Leu Asp
 225 230 235 240
 Glu Ala Ala Ala Arg Leu Leu Thr Val Pro Phe Glu Lys His Ser Thr
 245 250 255

Leu

<210> 698
 <211> 68
 <212> PRT
 <213> Homo sapiens

<400> 698
 Gln Tyr Lys Thr Pro Ala Val Asp Thr Thr Met Met Thr Phe His Glu
 1 5 10 15
 Leu Val Phe Leu Val Leu Thr Ala Lys Phe Val Leu Phe Thr Gly Gln
 20 25 30
 Ile Ser Asn Lys Val Leu Gly Leu Lys Ile His Gly Trp Thr Glu Val
 35 40 45
 Pro Tyr Pro Leu Thr Met Glu Ala Gly Ala Thr Phe Trp Gly Tyr Leu
 50 55 60
 Phe Leu Asn Phe
 65

<210> 699

673

<211> 360

<212> PRT

<213> Homo sapiens

<400> 699

Pro Cys Ser Ala Thr Thr Ala Trp Val Lys Ser Ser Ile Lys Thr His
1 5 10 15

Leu Cys Ala Ser Leu Arg His Ile Arg Phe Leu Leu Ser Val Cys Leu
20 25 30

Leu Cys Leu Val Ala Gly Thr Ala Val Ala Val Lys Met Ala Ser Thr
35 40 45

Ser Arg Leu Asp Ala Leu Pro Arg Val Thr Cys Pro Asn His Pro Asp
50 55 60

Ala Ile Leu Val Glu Asp Tyr Arg Ala Gly Asp Met Ile Cys Pro Glu
65 70 75 80

Cys Gly Leu Val Val Gly Asp Arg Val Ile Asp Val Gly Ser Glu Trp
85 90 95

Arg Thr Phe Ser Asn Asp Lys Ala Thr Lys Asp Pro Ser Arg Val Gly
100 105 110

Asp Ser Gln Asn Pro Leu Leu Ser Asp Gly Asp Leu Ser Thr Met Ile
115 120 125

Gly Lys Gly Thr Gly Ala Ala Ser Phe Asp Glu Phe Gly Asn Ser Lys
130 135 140

Tyr Gln Asn Arg Arg Thr Met Ser Ser Ser Asp Arg Ala Met Met Asn
145 150 155 160

Ala Phe Lys Glu Ile Thr Thr Met Ala Asp Arg Ile Asn Leu Pro Arg
165 170 175

Asn Ile Val Asp Arg Thr Asn Asn Leu Phe Lys Gln Val Tyr Glu Gln
180 185 190

Lys Ser Leu Lys Gly Arg Ala Asn Asp Ala Ile Ala Ser Ala Cys Leu
195 200 205

Tyr Ile Ala Cys Arg Gln Glu Gly Val Pro Arg Thr Phe Lys Glu Ile
210 215 220

Cys Ala Val Ser Arg Ile Ser Lys Lys Glu Ile Gly Arg Cys Phe Lys
225 230 235 240

Leu Ile Leu Lys Ala Leu Glu Thr Ser Val Asp Leu Ile Thr Thr Gly

674

245 250 255
Asp Phe Met Ser Arg Phe Cys Ser Asn Leu Cys Leu Pro Lys Gln Val
260 265 270
Gln Met Ala Ala Thr His Ile Ala Arg Lys Ala Val Glu Leu Asp Leu
275 280 285
Val Pro Gly Arg Ser Pro Ile Ser Val Ala Ala Ala Ile Tyr Met
290 295 300
Ala Ser Gln Ala Ser Ala Glu Lys Arg Thr Gln Lys Glu Ile Gly Asp
305 310 315 320
Ile Ala Gly Val Ala Asp Val Thr Ile Arg Gln Ser Tyr Arg Leu Ile
325 330 335
Tyr Pro Arg Ala Pro Asp Leu Phe Pro Thr Asp Phe Lys Phe Asp Thr
340 345 350
Pro Val Asp Lys Leu Pro Gln Leu
355 360

<210> 700
<211> 364
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (13)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (30)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (353)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (360)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 700

675

Pro Ser Trp Leu Arg Ala Arg Ser Ser Arg Ser Trp Xaa Ala Ser Pro
 1 5 10 15
 Arg Gly Pro Gln Pro Pro Arg Ile Arg Ala Arg Ser Ala Xaa Pro Met
 20 25 30
 Glu Gly Ala Arg Val Phe Gly Ala Leu Gly Pro Ile Gly Pro Ser Ser
 35 40 45
 Pro Gly Leu Thr Leu Gly Gly Leu Ala Val Ser Glu His Arg Leu Ser
 50 55 60
 Asn Lys Leu Leu Ala Trp Ser Gly Val Leu Glu Trp Gln Glu Lys Arg
 65 70 75 80
 Arg Pro Tyr Ser Asp Ser Thr Ala Lys Leu Lys Arg Thr Leu Pro Cys
 85 90 95
 Gln Ala Tyr Val Asn Gln Gly Glu Asn Leu Glu Thr Asp Gln Trp Pro
 100 105 110
 Gln Lys Leu Ile Met Gln Leu Ile Pro Gln Gln Leu Leu Thr Thr Leu
 115 120 125
 Gly Pro Leu Phe Arg Asn Ser Gln Leu Ala Gln Phe His Phe Thr Asn
 130 135 140
 Arg Asp Cys Asp Ser Leu Lys Gly Leu Cys Arg Ile Met Gly Asn Gly
 145 150 155 160
 Phe Ala Gly Cys Met Leu Phe Pro His Ile Ser Pro Cys Glu Val Arg
 165 170 175
 Val Leu Met Leu Leu Tyr Ser Ser Lys Lys Lys Ile Phe Met Gly Leu
 180 185 190
 Ile Pro Tyr Asp Gln Ser Gly Phe Val Ser Ala Ile Arg Gln Val Ile
 195 200 205
 Thr Thr Arg Lys Gln Ala Val Gly Pro Gly Gly Val Asn Ser Gly Pro
 210 215 220
 Val Gln Ile Val Asn Asn Lys Phe Leu Ala Trp Ser Gly Val Met Glu
 225 230 235 240
 Trp Gln Glu Pro Arg Pro Glu Pro Asn Ser Arg Ser Lys Arg Trp Leu
 245 250 255
 Pro Ser His Val Tyr Val Asn Gln Gly Glu Ile Leu Arg Thr Glu Gln
 260 265 270

676

Trp Pro Arg Lys Leu Tyr Met Gln Leu Ile Pro Gln Gln Leu Leu Thr
 275 280 285

Thr Leu Val Pro Leu Phe Arg Asn Ser Arg Leu Val Gln Phe His Phe
 290 295 300

Thr Lys Asp Leu Glu Thr Leu Lys Ser Leu Cys Arg Ile Met Asp Asn
 305 310 315 320

Gly Phe Ala Gly Cys Val His Phe Ser Tyr Lys Ala Ser Cys Glu Ile
 325 330 335

Arg Val Leu Met Leu Leu Tyr Ser Ser Glu Lys Lys Ile Phe Ile Gly
 340 345 350

Xaa Ile Pro His Asp Gln Gly Xaa Phe Val Gln Arg
 355 360

<210> 701

<211> 156

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (33)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 701

Gly Thr Arg Gly Ile Leu His Val Ala Val Pro Ala Arg Gly Thr His
 1 5 10 15

Ala Gln Cys Cys Arg Asn Trp Thr Val Pro Asp Ser Gly Gln Gly Lys
 20 25 30

Xaa Val Met Leu Glu Gly Gln Gly Arg Leu Glu Arg Val His Ile Pro
 35 40 45

Leu Ser Ala Pro Ala Ser Ala Thr Val Gln Arg Pro Thr Gly Pro Gln
 50 55 60

Pro Val Ala Cys Pro His Cys Pro Val Pro Thr Ser Asn Ser Pro Gln
 65 70 75 80

Pro Leu Val Ala Ser Val Pro Cys Pro Leu Gly Phe Ser Ser Gln Pro
 85 90 95

Ser Gly Leu Gly Leu Cys Arg Lys Val Met Pro Thr Gly Thr Leu Leu
 100 105 110

677

Thr Pro Gly Ser Phe Met Asp Val Val Ser Glu Leu Arg Thr Arg Gly
 115 120 125

Cys Gln Met Phe Leu Ala Pro His Val Ser Phe Arg Thr Glu Gln Lys
 130 135 140

His Lys Asp Ser Ala Lys Ser Ser Leu Tyr Ser Leu
 145 150 155

<210> 702

<211> 150

<212> PRT

<213> Homo sapiens

<400> 702

Ala Gly His Gly Leu Gly Val Arg Ala Gly Leu Lys Glu Phe Ala Thr
 1 5 10 15

Asn Leu Thr Glu Ser Gly Val His Gly Ala Leu Leu Ala Leu Asp Glu
 20 25 30

Thr Phe Asp Tyr Ser Asp Leu Ala Leu Leu Leu Gln Ile Pro Thr Gln
 35 40 45

Asn Ala Gln Ala Arg Gln Leu Leu Glu Lys Glu Phe Ser Asn Leu Ile
 50 55 60

Ser Leu Gly Thr Asp Arg Arg Leu Asp Glu Asp Ser Ala Lys Ser Phe
 65 70 75 80

Ser Arg Ser Pro Ser Trp Arg Lys Met Phe Arg Glu Lys Asp Leu Arg
 85 90 95

Gly Val Thr Pro Asp Ser Ala Glu Met Leu Pro Pro Asn Phe Arg Ser
 100 105 110

Ala Ala Ala Gly Ala Leu Gly Ser Pro Gly Leu Pro Leu Arg Lys Leu
 115 120 125

Gln Pro Glu Gly Gln Thr Ser Gly Ser Ser Arg Ala Asp Gly Val Ser
 130 135 140

Val Arg Thr Tyr Ser Cys
 145 150

<210> 703

<211> 527
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (243)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (257)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (259)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (471)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (477)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (480)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (484)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (511)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (519)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 703
Cys Val Cys Val Glu Gly Val Glu Gly Pro Arg Cys Asp Lys Cys Thr

679

| | | | |
|-------------|-----------------|-----------------|---------------------|
| 1 | 5 | 10 | 15 |
| Arg Gly Tyr | Ser Gly Val Phe | Pro Asp Cys Thr | Pro Cys His Gln Cys |
| 20 | 25 | 30 | |
| Phe Ala Leu | Trp Asp Val Ile | Ile Ala Glu Leu | Thr Asn Arg Thr His |
| 35 | 40 | 45 | |
| Arg Phe Leu | Glu Lys Ala Lys | Ala Leu Lys Ile | Ser Gly Val Ile Gly |
| 50 | 55 | 60 | |
| Pro Tyr Arg | Glu Thr Val Asp | Ser Val Glu Arg | Lys Val Ser Glu Ile |
| 65 | 70 | 75 | 80 |
| Lys Asp Ile | Leu Ala Gln Ser | Pro Ala Ala Glu | Pro Leu Lys Asn Ile |
| 85 | 90 | 95 | |
| Gly Asn Leu | Phe Glu Glu Ala | Glu Lys Leu Ile | Lys Asp Val Thr Glu |
| 100 | 105 | 110 | |
| Met Met Ala | Gln Val Glu Val | Lys Leu Ser Asp | Thr Thr Ser Gln Ser |
| 115 | 120 | 125 | |
| Asn Ser Thr | Ala Lys Glu Leu | Asp Ser Leu Gln | Thr Glu Ala Glu Ser |
| 130 | 135 | 140 | |
| Leu Asp Asn | Thr Val Lys Glu | Leu Ala Glu Gln | Leu Glu Phe Ile Lys |
| 145 | 150 | 155 | 160 |
| Asn Ser Asp | Ile Arg Gly Ala | Leu Asp Ser Ile | Thr Lys Tyr Phe Gln |
| 165 | 170 | 175 | |
| Met Ser Leu | Glu Ala Glu Glu | Arg Val Asn Ala | Ser Thr Thr Glu Pro |
| 180 | 185 | 190 | |
| Asn Ser Thr | Val Glu Gln Ser | Ala Leu Met Arg | Asp Arg Val Glu Asp |
| 195 | 200 | 205 | |
| Val Met Met | Glu Arg Glu Ser | Gln Phe Lys Glu | Lys Gln Glu Glu Gln |
| 210 | 215 | 220 | |
| Ala Arg Leu | Leu Asp Glu Leu | Ala Gly Lys Leu | Gln Ser Leu Asp Leu |
| 225 | 230 | 235 | 240 |
| Ser Ala Xaa | Ala Glu Met Thr | Cys Gly Thr Pro | Pro Gly Ala Ser Cys |
| 245 | 250 | 255 | |
| Xaa Glu Xaa | Glu Cys Gly Gly | Pro Asn Cys Arg | Thr Asp Glu Gly Glu |
| 260 | 265 | 270 | |
| Arg Lys Cys | Gly Gly Pro Gly | Cys Gly Gly Leu | Val Thr Val Ala His |

680

| | | |
|---|-----|---------|
| 275 | 280 | 285 |
| Asn Ala Trp Gln Lys Ala Met Asp Leu Asp Gln Asp Val Leu Ser Ala | | |
| 290 | 295 | 300 |
| Leu Ala Glu Val Glu Gln Leu Ser Lys Met Val Ser Glu Ala Lys Leu | | |
| 305 | 310 | 315 320 |
| Arg Ala Asp Glu Ala Lys Gln Ser Ala Glu Asp Ile Leu Leu Lys Thr | | |
| 325 | 330 | 335 |
| Asn Ala Thr Lys Glu Lys Met Asp Lys Ser Asn Glu Glu Leu Arg Asn | | |
| 340 | 345 | 350 |
| Leu Ile Lys Gln Ile Arg Asn Phe Leu Thr Gln Asp Ser Ala Asp Leu | | |
| 355 | 360 | 365 |
| Asp Ser Ile Glu Ala Val Ala Asn Glu Val Leu Lys Met Glu Met Pro | | |
| 370 | 375 | 380 |
| Ser Thr Pro Gln Gln Leu Gln Asn Leu Thr Glu Asp Ile Arg Glu Arg | | |
| 385 | 390 | 395 400 |
| Val Glu Ser Leu Ser Gln Val Glu Val Ile Leu Gln His Ser Ala Ala | | |
| 405 | 410 | 415 |
| Asp Ile Ala Arg Ala Glu Met Leu Leu Glu Glu Ala Lys Arg Ala Ser | | |
| 420 | 425 | 430 |
| Lys Ser Ala Thr Asp Val Lys Val Thr Ala Asp Met Val Lys Glu Ala | | |
| 435 | 440 | 445 |
| Leu Glu Glu Ala Glu Lys Ala Gln Val Ala Ala Glu Lys Ala Ile Lys | | |
| 450 | 455 | 460 |
| Gln Ala Asp Glu Asp Ile Xaa Arg Asn Pro Glu Pro Xaa Asn Phe Xaa | | |
| 465 | 470 | 475 480 |
| Leu Glu Phe Xaa Lys Gln Gln Leu Ser Gly Gly Asn Leu Val Gln Arg | | |
| 485 | 490 | 495 |
| Val Pro Arg Ala Ser Ser Glu Phe Arg Glu Asp Val Gly Arg Xaa Leu | | |
| 500 | 505 | 510 |
| Ser Gly Lys Leu Ala Gln Xaa Pro Gly Gly Gly Arg Ile Phe Trp | | |
| 515 | 520 | 525 |

<210> 704

<211> 62

681

<212> PRT

<213> Homo sapiens

<400> 704

Val Tyr Gln Arg Lys Ser Thr Val Val Leu Gly Gly Phe Leu Leu Trp
1 5 10 15

Asp Ile Asp Phe Leu Phe Phe Phe Arg Asn Ile Val Cys Cys Asn Leu
20 25 30

Asn Lys Asn Tyr Asp Ile Leu Arg Tyr Phe Ile Asp Lys Pro Asn Lys
35 40 45

Asn Ile Cys Phe Tyr Phe Lys Val Asn Val Phe Leu Phe Ser
50 55 60

<210> 705

<211> 44

<212> PRT

<213> Homo sapiens

<400> 705

Thr Glu Asp Leu Phe Gly Phe Lys His Leu Leu Arg Gln Tyr Leu Leu
1 5 10 15

Gly Lys Pro Asn Ile Ala Asn Gly Gln Phe Asp Phe Asn Phe Ser Lys
20 25 30

Asp Thr Leu Leu Ser Arg Arg Leu Lys Cys Leu His
35 40

<210> 706

<211> 193

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (1)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 706

Xaa Gly Arg Ala Trp Val Met Ala Ala Pro Gly Ala Leu Leu Val Met
1 5 10 15

Gly Val Ser Gly Ser Gly Lys Ser Thr Val Gly Ala Leu Leu Ala Ser
20 25 30

682

Glu Leu Gly Trp Lys Phe Tyr Asp Ala Asp Asp Tyr His Pro Glu Glu
35 40 45

Asn Arg Arg Lys Met Gly Lys Gly Ile Pro Leu Asn Asp Gln Asp Arg
50 55 60

Ile Pro Trp Leu Cys Asn Leu His Asp Ile Leu Leu Arg Asp Val Ala
65 70 75 80

Ser Gly Gln Arg Val Val Leu Ala Cys Ser Ala Leu Lys Lys Thr Tyr
85 90 95

Arg Asp Ile Leu Thr Gln Gly Lys Asp Gly Val Ala Leu Lys Cys Glu
100 105 110

Glu Ser Gly Lys Glu Ala Lys Gln Ala Glu Met Gln Leu Leu Val Val
115 120 125

His Leu Ser Gly Ser Phe Glu Val Ile Ser Gly Arg Leu Leu Lys Arg
130 135 140

Glu Gly His Phe Met Pro Pro Glu Leu Leu Gln Ser Gln Phe Glu Thr
145 150 155 160

Leu Glu Pro Pro Ala Ala Pro Glu Asn Phe Ile Gln Ile Ser Val Asp
165 170 175

Lys Asn Val Ser Glu Ile Ile Ala Thr Ile Met Glu Thr Leu Lys Met
180 185 190

Lys

<210> 707

<211> 121

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (102)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (103)

<223> Xaa equals any of the naturally occurring L-amino acids

683

<400> 707

Gly Ile Arg Gly Gln Thr Leu Trp Leu Gly Pro Leu Gly Ala Thr Leu
 1 5 10 15
 Trp Pro Leu Gly Ala Leu Glu Thr Ser His Val Leu Trp Ala Leu Trp
 20 25 30
 Arg Ala Leu Ala Leu His Gly Gly Ala Gly Arg His Cys Leu Pro Cys
 35 40 45
 Pro Leu Pro Ala Ala Pro Ala Leu Val Cys Arg Leu Gly Pro Gly Cys
 50 55 60
 Leu Leu Leu Gly Val Trp Pro Arg Ala Pro Val Lys Pro Trp Arg His
 65 70 75 80
 Cys Val Cys Val Met Gly Ser Glu Gly Leu Val Gly Ala Val His Trp
 85 90 95
 Ser Ser Ser Leu Pro Xaa Xaa Ala Ile Ser Met Ala Pro Phe Ala Ala
 100 105 110
 Glu Asp Thr His Cys Gly Ser Val Gly
 115 120

<210> 708

<211> 112

<212> PRT

<213> Homo sapiens

<400> 708

Asn Ser Phe Cys Tyr Phe His Ile Arg Val Gln Thr Tyr Lys Gly Ala
 1 5 10 15
 Cys Ser Leu Lys Val His Asn Tyr Ser Tyr Ser Val Cys Leu Tyr Cys
 20 25 30
 Tyr Arg Met Leu Cys Phe Gly Ala Leu Ser Ser Ala Asp Pro Arg Ser
 35 40 45
 Ser Val Glu Ile His Cys Leu Gly His Ser Leu Ile Arg Met Leu Ala
 50 55 60
 Gly Asp Phe Val Ser Asp Val Ala Ser Leu Phe Ser Val His Arg Leu
 65 70 75 80
 Arg Val Thr Thr Val Ala Cys Arg Val His Pro Val Gly Ala Ala Gln
 85 90 95

684

Leu Ser Glu Ser Lys Asn Leu Pro Thr Tyr Ser Asn Val Phe Ala Leu
100 105 110

<210> 709

<211> 72

<212> PRT

<213> Homo sapiens

<400> 709

Arg Arg Val Trp Val Leu Phe Pro Pro Gln Arg Pro Glu Ser Gly Trp
1 5 10 15

Gly Val Ser Pro Val Glu Gly Glu Thr Val Pro Ala Leu Arg Gly Met
20 25 30

Lys Lys Ser Val Gly Leu Pro Val Ala Val Gln Cys Val Ala Leu Pro
35 40 45

Trp Gln Glu Glu Leu Cys Leu Arg Phe Met Arg Glu Val Glu Arg Leu
50 55 60

Met Thr Pro Glu Lys Gln Ser Ser
65 70

<210> 710

<211> 84

<212> PRT

<213> Homo sapiens

<400> 710

Arg Leu His Arg Tyr Pro Glu Ala Met Ala Ser Lys Gly Leu Gln Asp
1 5 10 15

Leu Lys Gln Gln Val Glu Gly Thr Ala Gln Glu Ala Val Ser Ala Ala
20 25 30

Gly Ala Ala Ala Gln Gln Val Val Asp Gln Ala Thr Glu Ala Gly Gln
35 40 45

Lys Ala Met Asp Gln Leu Ala Lys Thr Thr Gln Glu Thr Ile Asp Lys
50 55 60

Thr Ala Asn Gln Ala Ser Asp Thr Phe Ser Gly Ile Gly Lys Lys Phe
65 70 75 80

685

Gly Leu Leu Lys

<210> 711

<211> 63

<212> PRT

<213> Homo sapiens

<400> 711

Arg Leu His Arg Tyr Pro Glu Ala Met Ala Ser Lys Gly Leu Gln Asp
1 5 10 15

Leu Lys Gln Gln Val Glu Gly Thr Ala Gln Glu Ala Ala Met Asp Gln
20 25 30

Leu Ala Lys Thr Thr Gln Glu Thr Ile Asp Lys Thr Ala Asn Gln Ala
35 40 45

Ser Asp Thr Phe Ser Gly Ile Gly Lys Lys Phe Gly Leu Leu Lys
50 55 60

<210> 712

<211> 86

<212> PRT

<213> Homo sapiens

<400> 712

Arg Leu Ala Asn Arg Ala Ile Met Ser His Lys Gln Ile Tyr Tyr Ser
1 5 10 15

Asp Lys Tyr Asp Asp Glu Glu Phe Glu Tyr Arg His Val Met Leu Pro
20 25 30

Lys Asp Ile Ala Lys Leu Val Pro Lys Thr His Leu Met Ser Glu Ser
35 40 45

Glu Trp Arg Asn Leu Gly Val Gln Gln Ser Gln Gly Trp Val His Tyr
50 55 60

Met Ile His Glu Pro Glu Pro His Ile Leu Leu Phe Arg Arg Pro Leu
65 70 75 80

Pro Lys Lys Pro Lys Lys
85

686

<210> 713
 <211> 193
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (129)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 713
 Val Gln Lys Ala Gly Ala Arg Ala Leu Ala Val Ala Gly Ala Ala Arg
 1 5 10 15
 Thr Pro Arg Ser Leu Pro Gly Arg Pro Ala Val Cys Asn Met Thr Leu
 20 25 30
 Glu Glu Phe Ser Ala Gly Glu Gln Lys Thr Glu Arg Met Asp Lys Val
 35 40 45
 Gly Asp Ala Leu Glu Glu Val Leu Ser Lys Ala Leu Ser Gln Arg Thr
 50 55 60
 Ile Thr Val Gly Val Tyr Glu Ala Ala Lys Leu Leu Asn Val Asp Pro
 65 70 75 80
 Asp Asn Val Val Leu Cys Leu Leu Ala Ala Asp Glu Asp Asp Asp Arg
 85 90 95
 Asp Val Ala Leu Gln Ile His Phe Thr Leu Ile Gln Ala Phe Cys Cys
 100 105 110
 Glu Asn Asp Ile Asn Ile Leu Arg Val Thr Thr Arg Ala Gly Trp Arg
 115 120 125
 Xaa Pro Ala Leu Gly Asp Arg Arg Trp Pro Arg Gly Glu Arg Gly Arg
 130 135 140
 Arg Ala Ala Pro Gly Pro Ala Leu Arg Val Val Thr Asn Pro His Ser
 145 150 155 160
 Ser Gln Trp Lys Asp Pro Ala Leu Ser Gln Leu Ile Cys Phe Cys Arg
 165 170 175
 Glu Ser Arg Tyr Met Asp Gln Trp Val Pro Val Ile Asn Leu Pro Glu
 180 185 190

Arg

687

<210> 714
<211> 200
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (90)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (93)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (190)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 714
Gly Pro Gly Ala Cys Ser Gly Pro Ala Pro Ser Pro Arg Arg Pro Gln
1 5 10 15
Ser Val Lys Cys Glu Pro Arg Arg Arg Gly Ile Trp Pro Gly Ala
20 25 30
Gly Gly Gly Val Gly Ala Ala Arg His Val His His His Gln Gly Ala
35 40 45
Gln Gln Ala Gly Arg Ala Ala Pro His Arg Ser His Ala Ala Ala Gly
50 55 60
Gly Gly Pro Ala Arg Arg Ala Pro Glu Met Pro Ala Ala Arg Ala Ala
65 70 75 80
Asp Leu Ala Ala Pro Ala Gly Ala Ala Xaa Cys Ala Xaa Pro Gly Pro
85 90 95
Trp Pro Leu Ser Ser Pro Gly Pro Arg Leu Val Phe Asn Arg Val Asn
100 105 110
Gly Arg Arg Ala Pro Ser Thr Ser Pro Ser Phe Glu Gly Thr Gln Glu
115 120 125
Thr Tyr Thr Val Ala His Glu Glu Asn Val Arg Phe Val Ser Glu Ala
130 135 140
Trp Gln Gln Val Gln Gln Gln Leu Asp Gly Gly Pro Ala Gly Glu Gly

688

145 150 155 160
 Gly Pro Arg Pro Val Gln Tyr Val Glu Arg Thr Pro Asn Pro Arg Leu
 165 170 175
 Gln Asn Phe Val Pro Ile Asp Leu Asp Glu Trp Trp Ala Xaa Gln Phe
 180 185 190
 Leu Ala Arg Ile Thr Ser Cys Ser
 195 200

<210> 715

<211> 106

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (15)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 715

Trp Ile Pro Arg Ala Ala Gly Ile Arg His Glu Leu Val Pro Xaa Leu
 1 5 10 15

Trp Ser Arg Glu Glu Ala Met Ala Thr Met Glu Asn Lys Val Ile Cys
 20 25 30

Ala Leu Val Leu Val Ser Met Leu Ala Leu Gly Thr Leu Ala Glu Ala
 35 40 45

Gln Thr Glu Thr Cys Thr Val Ala Pro Arg Glu Arg Gln Asn Cys Gly
 50 55 60

Phe Pro Gly Val Thr Pro Ser Gln Cys Ala Asn Lys Gly Cys Cys Phe
 65 70 75 80

Asp Asp Thr Val Arg Gly Val Pro Trp Cys Phe Tyr Pro Asn Thr Ile
 85 90 95

Asp Val Pro Pro Glu Glu Glu Cys Glu Phe
 100 105

<210> 716

<211> 105

<212> PRT

<213> Homo sapiens

689

<400> 716

Glu Gly Arg Glu Ala Gly Ser Gly Leu Ser Val Asp Ser Arg Asp Lys
 1 5 10 15

Gly His Glu Gly Arg Gly Leu Gly Pro Phe Arg Ile Pro Gln Asp Ser
 20 25 30

Gln Val Gln Leu Cys Gln Lys Gly Thr Phe His Val Met Gln Leu Arg
 35 40 45

Gly Leu Ser Leu Asn Pro Arg Leu Leu Leu Thr Leu Gly Ser Phe Asn
 50 55 60

Gln Val Gly Gln Pro Leu Leu Gln Arg Gly Val Gly Trp Leu Ser Ser
 65 70 75 80

Leu Ser His Ala Ala Cys Glu Asp Arg Gly Gly Gly Val Gly Ser Gly
 85 90 95

Lys Ser Pro Glu Asn Arg Arg Gly Ile
 100 105

<210> 717

<211> 431

<212> PRT

<213> Homo sapiens

<400> 717

Arg Ala Ala Gly Ile Arg His Glu Arg Gly Gly Pro Thr Gly Ser Cys
 1 5 10 15

Pro Gly Leu Pro Ser Pro Pro Met Val Leu Tyr Ile Lys Tyr Pro Gly
 20 25 30

Trp Arg Ser His Met Leu Leu Thr Glu Gly Gly Asn Tyr His Ser Ser
 35 40 45

Leu Gly Thr Arg Cys Glu Leu Ser Cys Asp Arg Gly Phe Arg Leu Ile
 50 55 60

Gly Arg Arg Ser Val Gln Cys Leu Pro Ser Arg Arg Trp Ser Gly Thr
 65 70 75 80

Ala Tyr Cys Arg Gln Met Arg Cys His Ala Leu Pro Phe Ile Thr Ser
 85 90 95

Gly Thr Tyr Thr Cys Thr Asn Gly Val Leu Leu Asp Ser Arg Cys Asp
 100 105 110

690

Tyr Ser Cys Ser Ser Gly Tyr His Leu Glu Gly Asp Arg Ser Arg Ile
 115 120 125
 Cys Met Glu Asp Gly Arg Trp Ser Gly Gly Glu Pro Val Cys Val Asp
 130 135 140
 Ile Asp Pro Pro Lys Ile Arg Cys Pro His Ser Arg Glu Lys Met Ala
 145 150 155 160
 Glu Pro Glu Lys Leu Thr Ala Arg Val Tyr Trp Asp Pro Pro Leu Val
 165 170 175
 Lys Asp Ser Ala Asp Gly Thr Ile Thr Arg Val Thr Leu Arg Gly Pro
 180 185 190
 Glu Pro Gly Ser His Phe Pro Glu Gly Glu His Val Ile Arg Tyr Thr
 195 200 205
 Ala Tyr Asp Arg Ala Tyr Asn Arg Ala Ser Cys Lys Phe Ile Val Lys
 210 215 220
 Val Gln Val Arg Arg Cys Pro Thr Leu Lys Pro Pro Gln His Gly Tyr
 225 230 235 240
 Leu Thr Cys Thr Ser Ala Gly Asp Asn Tyr Gly Ala Thr Cys Glu Tyr
 245 250 255
 His Cys Asp Gly Gly Tyr Asp Arg Gln Gly Thr Pro Ser Arg Val Cys
 260 265 270
 Gln Ser Ser Arg Gln Trp Ser Gly Ser Pro Pro Ile Cys Ala Pro Met
 275 280 285
 Lys Ile Asn Val Asn Val Asn Ser Ala Ala Gly Leu Leu Asp Gln Phe
 290 295 300
 Tyr Glu Lys Gln Arg Leu Leu Ile Ile Ser Ala Pro Asp Pro Ser Asn
 305 310 315 320
 Arg Tyr Tyr Lys Met Gln Ile Ser Met Leu Gln Gln Ser Thr Cys Gly
 325 330 335
 Leu Asp Leu Arg His Val Thr Ile Ile Glu Leu Val Gly Gln Pro Pro
 340 345 350
 Gln Glu Val Gly Arg Ile Arg Glu Gln Gln Leu Ser Ala Asn Ile Ile
 355 360 365
 Glu Glu Leu Arg Gln Phe Gln Arg Leu Thr Arg Ser Tyr Phe Asn Met
 370 375 380

691

Val Leu Ile Asp Lys Gln Gly Ile Asp Arg Asp Arg Tyr Met Glu Pro
 385 390 395 400

Val Thr Pro Glu Glu Ile Phe Thr Phe Ile Asp Asp Tyr Leu Leu Ser
 405 410 415

Asn Gln Glu Leu Thr Gln Arg Arg Glu Gln Arg Asp Ile Cys Glu
 420 425 430

<210> 718

<211> 417

<212> PRT

<213> Homo sapiens

<400> 718

Gln Gly Leu Pro Asp Gly Val Trp Ala His Gly Thr Cys Pro Gly His
 1 5 10 15

Arg Leu Val Ser Ser Gln Arg Arg Ile Ile Ala Ser Gly Ser Glu Asp
 20 25 30

Cys Thr Val Met Val Trp Gln Ile Pro Glu Asn Gly Leu Thr Ser Pro
 35 40 45

Leu Thr Glu Pro Val Val Val Leu Glu Gly His Thr Lys Arg Val Gly
 50 55 60

Ile Ile Ala Trp His Pro Thr Ala Arg Asn Val Leu Leu Ser Ala Gly
 65 70 75 80

Cys Asp Asn Val Val Leu Ile Trp Asn Val Gly Thr Ala Glu Glu Leu
 85 90 95

Tyr Arg Leu Asp Ser Leu His Pro Asp Leu Ile Tyr Asn Val Ser Trp
 100 105 110

Asn His Asn Gly Ser Leu Phe Cys Ser Ala Cys Lys Asp Lys Ser Val
 115 120 125

Arg Ile Ile Asp Pro Arg Arg Gly Thr Leu Val Ala Glu Arg Glu Lys
 130 135 140

Ala His Glu Gly Ala Arg Pro Met Arg Ala Ile Phe Leu Ala Asp Gly
 145 150 155 160

Lys Val Phe Thr Thr Gly Phe Ser Arg Met Ser Glu Arg Gln Leu Ala
 165 170 175

692

Leu Trp Asp Pro Glu Asn Leu Glu Glu Pro Met Ala Leu Gln Glu Leu
180 185 190

Asp Ser Ser Asn Gly Ala Leu Leu Pro Phe Tyr Asp Pro Asp Thr Ser
195 200 205

Val Val Tyr Val Cys Gly Lys Gly Asp Ser Ser Ile Arg Tyr Phe Glu
210 215 220

Ile Thr Glu Glu Pro Pro Tyr Ile His Phe Leu Asn Thr Phe Thr Ser
225 230 235 240

Lys Glu Pro Gln Arg Gly Met Gly Ser Met Pro Lys Arg Gly Leu Glu
245 250 255

Val Ser Lys Cys Glu Ile Ala Arg Phe Tyr Lys Leu His Glu Arg Lys
260 265 270

Cys Glu Pro Ile Val Met Thr Val Pro Arg Lys Ser Asp Leu Phe Gln
275 280 285

Asp Asp Leu Tyr Pro Asp Thr Ala Gly Pro Glu Ala Ala Leu Glu Ala
290 295 300

Glu Glu Trp Val Ser Gly Arg Asp Ala Asp Pro Ile Leu Ile Ser Leu
305 310 315 320

Arg Glu Ala Tyr Val Pro Ser Lys Gln Arg Asp Leu Lys Ile Ser Arg
325 330 335

Arg Asn Val Leu Ser Asp Ser Arg Pro Ala Met Ala Pro Gly Ser Ser
340 345 350

His Leu Gly Ala Pro Ala Ser Thr Thr Thr Ala Ala Asp Ala Thr Pro
355 360 365

Ser Gly Ser Leu Ala Arg Ala Gly Glu Ala Gly Lys Leu Glu Glu Val
370 375 380

Met Gln Glu Leu Arg Ala Leu Arg Ala Leu Val Lys Glu Gln Gly Asp
385 390 395 400

Arg Ile Cys Arg Leu Glu Glu Gln Leu Gly Arg Met Glu Asn Gly Asp
405 410 415

Ala

<210> 719

693

<211> 290
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (7)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (74)
 <223> Xaa equals any of the naturally occurring L-amino acids

<220>
 <221> SITE
 <222> (131)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 719
 Glu Leu Ser Ala Ser Ala Xaa Asp Asp Gly Asn Phe Ser Leu Leu Ile
 1 5 10 15
 Arg Ala Val Glu Glu Thr Asp Ala Gly Leu Tyr Thr Cys Asn Leu His
 20 25 30
 His His Tyr Cys His Leu Tyr Glu Ser Leu Ala Val Arg Leu Glu Val
 35 40 45
 Thr Asp Gly Pro Pro Ala Pro Pro Pro Thr Gly Thr Ala Arg Arg Arg
 50 55 60
 Cys Trp Arg Trp Arg Ala Ala Pro Ala Xaa Leu Thr Cys Val Asn Arg
 65 70 75 80
 Gly His Val Trp Thr Asp Arg His Val Glu Glu Ala Gln Gln Val Val
 85 90 95
 His Trp Asp Arg Gln Pro Pro Gly Val Pro His Asp Arg Ala Asp Arg
 100 105 110
 Leu Leu Asp Leu Tyr Ala Ser Ala Ser Ala Ala Leu Arg Ala Pro Phe
 115 120 125
 Ser Ala Xaa Arg Val Ala Val Gly Ala Asp Ala Phe Lys Arg Gly Asp
 130 135 140
 Phe Ser Leu Arg Ile Glu Pro Leu Glu Val Ala Asp Glu Gly Thr Tyr
 145 150 155 160
 Ser Cys His Leu His His His Tyr Trp Arg Ala Ala Thr Thr Ser Ser

694

165 170 175
 Met Ser Ser Ser Pro Arg Ala Glu Pro Thr Ser Ser Ser Trp Ala
 180 185 190
 Thr Cys Trp Pro Arg Cys Cys Ser Ser Ser Cys Tyr Trp Ser Leu Ser
 195 200 205
 Ser Trp Pro Pro Ala Gly Arg Gly Gly Tyr Glu Tyr Ser Asp Gln Lys
 210 215 220
 Ser Gly Lys Ser Lys Gly Lys Asp Val Asn Leu Ala Glu Phe Ala Val
 225 230 235 240
 Ala Ala Gly Asp Gln Met Leu Tyr Arg Ser Glu Asp Ile Gln Leu Asp
 245 250 255
 Tyr Lys Asn Asn Ile Leu Lys Glu Arg Ala Glu Leu Ala His Ser Pro
 260 265 270
 Leu Pro Ala Lys Tyr Ile Asp Leu Asp Lys Gly Phe Arg Lys Glu Asn
 275 280 285
 Cys Lys
 290

<210> 720
 <211> 459
 <212> PRT
 <213> Homo sapiens

<220>
 <221> SITE
 <222> (50)
 <223> Xaa equals any of the naturally occurring L-amino acids

<400> 720
 Asp Ala His Pro Lys Pro Cys Cys Glu Thr Ser Ala Ala Ala Cys Arg
 1 5 10 15
 Leu Val Glu Arg Ile Leu Thr Ser Trp Glu Glu Asn Asp Arg Val Gln
 20 25 30
 Cys Ala Gly Gly Pro Arg Lys Gly Tyr Met Gly His Leu Thr Arg Val
 35 40 45
 Ala Xaa Ala Leu Val Gln Asn Thr Glu Lys Gly Pro Asn Ala Glu Gln
 50 55 60

695

Leu Arg Gln Leu Leu Lys Glu Leu Pro Ser Glu Gln Gln Glu Gln Trp
 65 70 75 80
 Glu Ala Phe Val Ser Gly Pro Leu Ala Glu Thr Asn Lys Lys Asn Met
 85 90 95
 Val Asp Leu Val Asn Thr His His Leu His Ser Ser Ser Asp Asp Glu
 100 105 110
 Asp Asp Arg Leu Lys Glu Phe Asn Phe Pro Glu Glu Ala Val Leu Gln
 115 120 125
 Gln Ala Phe Met Asp Phe Gln Met Gln Arg Met Thr Ser Ala Phe Ile
 130 135 140
 Asp His Phe Gly Phe Asn Asp Glu Glu Phe Gly Glu Gln Glu Glu Ser
 145 150 155 160
 Val Asn Ala Pro Phe Asp Lys Thr Ala Asn Ile Thr Phe Ser Leu Asn
 165 170 175
 Ala Asp Asp Glu Asn Pro Asn Ala Asn Leu Leu Glu Ile Cys Tyr Lys
 180 185 190
 Asp Arg Ile Gln Gln Phe Asp Asp Asp Glu Glu Glu Glu Asp Glu Glu
 195 200 205
 Glu Ala Gln Gly Ser Gly Glu Ser Asp Gly Glu Asp Gly Ala Trp Gln
 210 215 220
 Gly Ser Gln Leu Ala Arg Gly Ala Arg Leu Gly Gln Pro Pro Gly Val
 225 230 235 240
 Arg Ser Gly Gly Ser Thr Asp Ser Glu Asp Glu Glu Glu Glu Asp Glu
 245 250 255
 Glu Glu Glu Glu Asp Glu Glu Gly Ile Gly Cys Ala Ala Arg Gly Gly
 260 265 270
 Ala Thr Pro Leu Ser Tyr Pro Ser Pro Gly Pro Gln Pro Pro Gly Pro
 275 280 285
 Ser Trp Thr Ala Thr Phe Asp Pro Val Pro Thr Asp Ala Pro Thr Ser
 290 295 300
 Pro Arg Val Ser Gly Glu Glu Glu Leu His Thr Gly Pro Pro Ala Pro
 305 310 315 320
 Gln Gly Pro Leu Ser Val Pro Gln Gly Leu Pro Thr Gln Ser Leu Ala
 325 330 335

Ser Pro Pro Ala Arg Asp Ala Leu Gln Leu Arg Ser Gln Asp Pro Thr
340 345 350

Pro Pro Ser Ala Pro Gln Glu Ala Thr Glu Gly Ser Lys Val Thr Glu
355 360 365

Pro Ser Ala Pro Cys Gln Ala Leu Val Ser Ile Gly Asp Leu Gln Ala
370 375 380

Thr Phe His Gly Ile Arg Ser Ala Pro Ser Ser Ser Asp Ser Ala Thr
385 390 395 400

Arg Asp Pro Ser Thr Ser Val Pro Ala Ser Gly Ala His Gln Pro Pro
405 410 415

Gln Thr Thr Glu Gly Glu Lys Ser Pro Glu Pro Leu Gly Leu Pro Gln
420 425 430

Ser Gln Ser Ala Gln Ala Leu Thr Pro Pro Pro Ile Pro Asn Gly Ser
435 440 445

Ala Pro Glu Gly Pro Ala Ser Pro Gly Ser Gln
450 455

<210> 721
<211> 523
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (12)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (115)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (194)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (327)
<223> Xaa equals any of the naturally occurring L-amino acids

<400> 721

Leu Gln Arg Leu Lys Leu Ile Lys Pro Leu Leu Xaa Phe Glu Ser Leu
1 5 10 15

Glu Glu Cys Tyr Met Ala Lys Ile Leu Val Ala Glu Gly Thr Arg Asp
20 25 30

Val Pro Ile Gly Ala Ile Ile Cys Ile Thr Val Gly Lys Pro Glu Asp
35 40 45

Ile Glu Ala Phe Lys Asn Tyr Thr Leu Asp Ser Ser Ala Ala Pro Thr
50 55 60

Pro Gln Ala Ala Pro Ala Pro Thr Pro Ala Ala Thr Ala Ser Pro Pro
65 70 75 80

Thr Pro Ser Ala Gln Ala Pro Gly Ser Ser Tyr Pro Pro His Met Gln
85 90 95

Val Leu Leu Pro Ala Leu Ser Pro Thr Met Thr Met Gly Thr Val Gln
100 105 110

Arg Trp Xaa Lys Lys Val Gly Glu Lys Leu Ser Glu Gly Asp Leu Leu
115 120 125

Ala Glu Ile Glu Thr Asp Lys Ala Thr Ile Gly Phe Glu Val Gln Glu
130 135 140

Glu Gly Tyr Leu Ala Lys Ile Leu Val Pro Glu Gly Thr Arg Asp Val
145 150 155 160

Pro Leu Gly Thr Pro Leu Cys Ile Ile Val Glu Lys Glu Ala Asp Ile
165 170 175

Ser Ala Phe Ala Asp Tyr Arg Pro Thr Glu Val Thr Asp Leu Lys Pro
180 185 190

Gln Xaa Pro Pro Pro Thr Pro Pro Pro Val Ala Ala Val Pro Pro Thr
195 200 205

Pro Gln Pro Leu Ala Pro Thr Pro Ser Ala Pro Cys Pro Ala Thr Pro
210 215 220

Ala Gly Pro Lys Gly Arg Val Phe Val Ser Pro Leu Ala Lys Lys Leu
225 230 235 240

Ala Val Glu Lys Gly Ile Asp Leu Thr Gln Val Lys Gly Thr Gly Pro
245 250 255

Asp Gly Arg Ile Thr Lys Lys Asp Ile Asp Ser Phe Val Pro Ser Lys
260 265 270

Val Ala Pro Ala Pro Ala Ala Val Val Pro Pro Thr Gly Pro Gly Met
275 280 285

Ala Pro Val Pro Thr Gly Val Phe Thr Asp Ile Pro Ile Ser Asn Ile
290 295 300

Arg Arg Val Ile Ala Gln Arg Leu Met Gln Ser Lys Gln Thr Ile Pro
305 310 315 320

His Tyr Tyr Leu Ser Ile Xaa Val Asn Met Gly Glu Val Leu Leu Val
325 330 335

Arg Lys Glu Leu Asn Lys Ile Leu Glu Gly Arg Ser Lys Ile Ser Val
340 345 350

Asn Asp Phe Ile Ile Lys Ala Ser Ala Leu Ala Cys Leu Lys Val Pro
355 360 365

Glu Ala Asn Ser Ser Trp Met Asp Thr Val Ile Arg Gln Asn His Val
370 375 380

Val Asp Val Ser Val Ala Val Ser Thr Pro Ala Gly Leu Ile Thr Pro
385 390 395 400

Ile Val Phe Asn Ala His Ile Lys Gly Val Glu Thr Ile Ala Asn Asp
405 410 415

Val Val Ser Leu Ala Thr Lys Ala Arg Glu Gly Lys Leu Gln Pro His
420 425 430

Glu Phe Gln Gly Gly Thr Phe Thr Ile Ser Asn Leu Gly Met Phe Gly
435 440 445

Ile Lys Asn Phe Ser Ala Ile Ile Asn Pro Pro Gln Ala Cys Ile Leu
450 455 460

Ala Ile Gly Ala Ser Glu Asp Lys Leu Val Pro Ala Asp Asn Glu Lys
465 470 475 480

Gly Phe Asp Val Ala Ser Met Met Ser Val Thr Leu Ser Cys Asp His
485 490 495

Arg Val Val Asp Gly Ala Val Gly Ala Gln Trp Leu Ala Glu Phe Arg
500 505 510

Lys Tyr Leu Glu Lys Pro Ile Thr Met Leu Leu
515 520

699

<210> 722

<211> 111

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (10)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 722

Ser Ser Arg Ser Arg Ala Ala Asp Glu Xaa Ala Leu Cys Leu Gln Cys
1 5 10 15

Asp Met Asn Asp Cys Tyr Ser Arg Leu Arg Arg Leu Val Pro Thr Ile
20 25 30

Pro Pro Asn Lys Lys Val Ser Lys Val Glu Ile Leu Gln His Val Ile
35 40 45

Asp Tyr Ile Leu Asp Leu Gln Leu Ala Leu Glu Thr His Pro Ala Leu
50 55 60

Leu Arg Gln Pro Pro Pro Pro Ala Pro Pro His His Pro Ala Gly Thr
65 70 75 80

Cys Pro Ala Ala Pro Pro Arg Thr Pro Leu Thr Ala Leu Asn Thr Asp
85 90 95

Pro Ala Gly Ala Val Asn Lys Gln Gly Asp Ser Ile Leu Cys Arg
100 105 110

<210> 723

<211> 190

<212> PRT

<213> Homo sapiens

<400> 723

Ser Gly Gly Gly Gly Gly Arg Met Ile Lys Leu Phe Ser Leu Lys Gln
1 5 10 15

Gln Lys Lys Glu Glu Glu Ser Ala Gly Gly Thr Lys Gly Ser Ser Lys
20 25 30

Lys Ala Ser Ala Ala Gln Leu Arg Ile Gln Lys Asp Ile Asn Glu Leu
35 40 45

Asn Leu Pro Lys Thr Cys Asp Ile Ser Phe Ser Asp Pro Asp Asp Leu
50 55 60

Leu Asn Phe Lys Leu Val Ile Cys Pro Asp Glu Gly Phe Tyr Lys Ser
65 70 75 80

Gly Lys Phe Val Phe Ser Phe Lys Val Gly Gln Gly Tyr Pro His Asp
85 90 95

Pro Pro Lys Val Lys Cys Glu Thr Met Val Tyr His Pro Asn Ile Asp
100 105 110

Leu Glu Gly Asn Val Cys Leu Asn Ile Leu Arg Glu Asp Trp Lys Pro
115 120 125

Val Leu Thr Ile Asn Ser Ile Ile Tyr Gly Leu Gln Tyr Leu Phe Leu
130 135 140

Glu Pro Asn Pro Glu Asp Pro Leu Asn Lys Glu Ala Ala Glu Val Leu
145 150 155 160

Gln Asn Asn Arg Arg Leu Phe Glu Gln Asn Val Gln Arg Ser Met Arg
165 170 175

Gly Gly Tyr Ile Gly Ser Thr Tyr Phe Glu Arg Cys Leu Lys
180 185 190

<210> 724

<211> 524

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (247)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (417)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (440)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (443)

<223> Xaa equals any of the naturally occurring L-amino acids

701

<400> 724

Arg Arg Arg Arg Ala Asp Arg Ala Thr Pro Arg Glu Val Leu Glu Thr
 1 5 10 15
 Pro Gly Ala Ala Ser Val Gln Thr Leu Pro Ser Val Thr Met Lys Leu
 20 25 30
 Trp Val Ser Ala Leu Leu Met Ala Trp Phe Gly Val Leu Ser Cys Val
 35 40 45
 Gln Ala Glu Phe Phe Thr Ser Ile Gly His Met Thr Asp Leu Ile Tyr
 50 55 60
 Ala Glu Lys Glu Leu Val Gln Ser Leu Lys Glu Tyr Ile Leu Val Glu
 65 70 75 80
 Glu Ala Lys Leu Ser Lys Ile Lys Ser Trp Ala Asn Lys Met Glu Ala
 85 90 95
 Leu Thr Ser Lys Ser Ala Ala Asp Ala Glu Gly Tyr Leu Ala His Pro
 100 105 110
 Val Asn Ala Tyr Lys Leu Val Lys Arg Leu Asn Thr Asp Trp Pro Ala
 115 120 125
 Leu Glu Asp Leu Val Leu Gln Asp Ser Ala Ala Gly Phe Ile Ala Asn
 130 135 140
 Leu Ser Val Gln Arg Gln Phe Phe Pro Thr Asp Glu Asp Glu Ile Gly
 145 150 155 160
 Ala Ala Lys Ala Leu Met Arg Leu Gln Asp Thr Tyr Arg Leu Asp Pro
 165 170 175
 Gly Thr Ile Ser Arg Gly Glu Leu Pro Gly Thr Lys Tyr Gln Ala Met
 180 185 190
 Leu Ser Val Asp Asp Cys Phe Gly Met Gly Arg Ser Ala Tyr Asn Glu
 195 200 205
 Gly Asp Tyr Tyr His Thr Val Leu Trp Met Glu Gln Val Leu Lys Gln
 210 215 220
 Leu Asp Ala Gly Glu Glu Ala Thr Thr Thr Lys Ser Gln Val Leu Asp
 225 230 235 240
 Tyr Leu Ser Tyr Ala Val Xaa Gln Leu Gly Asp Leu His Arg Ala Leu
 245 250 255
 Glu Leu Thr Arg Arg Leu Leu Ser Leu Asp Pro Ser His Glu Arg Ala

| 260 | 265 | 270 |
|---|-----|-------------|
| Gly Gly Asn Leu Arg Tyr Phe Glu Gln Leu Leu Glu Glu Glu Arg Glu | | |
| 275 | 280 | 285 |
| Lys Thr Leu Thr Asn Gln Thr Glu Ala Glu Leu Ala Thr Pro Glu Gly | | |
| 290 | 295 | 300 |
| Ile Tyr Glu Arg Pro Val Asp Tyr Leu Pro Glu Arg Asp Val Tyr Glu | | |
| 305 | 310 | 315 320 |
| Ser Leu Cys Arg Gly Glu Gly Val Lys Leu Thr Pro Arg Arg Gln Lys | | |
| | 325 | 330 335 |
| Arg Leu Phe Cys Arg Tyr His His Gly Asn Arg Ala Pro Gln Leu Leu | | |
| | 340 | 345 350 |
| Ile Ala Pro Phe Lys Glu Glu Asp Glu Trp Asp Ser Pro His Ile Val | | |
| | 355 | 360 365 |
| Arg Tyr Tyr Asp Val Met Ser Asp Glu Glu Ile Glu Arg Ile Lys Glu | | |
| | 370 | 375 380 |
| Ile Ala Lys Pro Lys Leu Ala Arg Ala Thr Val Arg Asp Pro Lys Thr | | |
| | 385 | 390 395 400 |
| Gly Val Leu Thr Val Ala Ser Tyr Arg Val Ser Lys Ser Ser Trp Leu | | |
| | 405 | 410 415 |
| Xaa Glu Asp Asp Asp Pro Val Val Ala Arg Val Asn Arg Arg Met Gln | | |
| | 420 | 425 430 |
| His Ile Thr Gly Leu Thr Val Xaa Thr Ala Xaa Leu Leu Gln Val Ala | | |
| | 435 | 440 445 |
| Asn Tyr Gly Val Gly Gly Gln Tyr Glu Pro His Phe Asp Phe Ser Arg | | |
| | 450 | 455 460 |
| Asn Asp Glu Arg Asp Thr Phe Lys His Leu Gly Thr Gly Asn Arg Val | | |
| | 465 | 470 475 480 |
| Ala Thr Phe Leu Asn Tyr Met Ser Asp Val Glu Ala Gly Gly Ala Thr | | |
| | 485 | 490 495 |
| Val Phe Pro Asp Leu Gly Ala Ala Ile Trp Pro Lys Lys Gly Thr Ala | | |
| | 500 | 505 510 |
| Val Phe Trp Tyr Asn Leu Leu Arg Ser Gly Arg Arg | | |
| | 515 | 520 |

703

<210> 725
<211> 92
<212> PRT
<213> Homo sapiens

<400> 725
Leu Lys Met Thr Ser Leu Phe Ala Gln Glu Ile Arg Leu Ser Lys Arg
1 5 10 15
His Glu Glu Ile Val Ser Gln Arg Leu Met Leu Leu Gln Gln Met Glu
20 25 30
Asn Lys Leu Gly Asp Gln His Thr Glu Lys Ala Ser Gln Leu Gln Thr
35 40 45
Val Glu Thr Ala Phe Lys Arg Asn Leu Ser Leu Leu Lys Asp Ile Glu
50 55 60
Ala Ala Glu Lys Ser Leu Gln Thr Arg Ile His Pro Leu Pro Arg Pro
65 70 75 80
Glu Val Val Ser Leu Glu Thr Arg Tyr Trp Ala Ser
85 90

<210> 726
<211> 690
<212> PRT
<213> Homo sapiens

<220>
<221> SITE
<222> (108)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (123)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (383)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>
<221> SITE
<222> (688)
<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (690)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 726

| | | | | | | | | | | | | | | | |
|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Val | Ser | Arg | Ser | Pro | Arg | Val | Pro | Leu | Pro | Pro | Arg | Ser | Phe | Ser | Arg |
| 1 | | | | 5 | | | | | 10 | | | | | 15 | |
| Met | Ala | Gly | Asp | Ser | Thr | Ala | Thr | Ser | Arg | Arg | Leu | Gly | Ala | Ala | Pro |
| | | | 20 | | | | | | 25 | | | | | 30 | |
| Asp | Arg | Ala | Ala | Pro | His | Ile | Leu | Pro | Ala | Gly | Ala | His | Arg | Ala | Ala |
| | | | 35 | | | | | 40 | | | | | 45 | | |
| Thr | Ala | Pro | Gly | Leu | Gly | Gly | Gly | Pro | Glu | Pro | Leu | Gly | Arg | Ala | Leu |
| | | | 50 | | | | 55 | | | | | | 60 | | |
| Ala | Gly | Gly | Leu | Arg | Gly | Pro | Gln | Gly | Asn | Gly | Trp | Leu | Gln | Glu | Arg |
| | | | 65 | | | 70 | | | | 75 | | | | | 80 |
| Lys | Arg | Arg | Cys | Pro | Gly | Leu | Ala | Gly | Cys | Phe | Glu | Ala | Ile | Ser | Cys |
| | | | | 85 | | | | | 90 | | | | | | 95 |
| Gly | Thr | Gly | Leu | Gly | Leu | Pro | Gly | Leu | Ala | Leu | Xaa | Arg | Glu | Leu | Ile |
| | | | 100 | | | | | 105 | | | | | | 110 | |
| Ser | Trp | Gly | Ala | Pro | Gly | Ser | Ala | Asp | Ser | Xaa | Arg | Leu | Leu | His | Trp |
| | | | 115 | | | | | 120 | | | | | | 125 | |
| Gly | Ser | His | Pro | Thr | Ala | Phe | Val | Val | Ser | Tyr | Ala | Ala | Ala | Leu | Pro |
| | | | 130 | | | | | 135 | | | | | | 140 | |
| Ala | Ala | Ala | Leu | Trp | His | Lys | Leu | Gly | Ser | Leu | Trp | Val | Pro | Gly | Gly |
| | | | 145 | | | | 150 | | | | 155 | | | | 160 |
| Gln | Gly | Gly | Ser | Gly | Asn | Pro | Val | Arg | Arg | Leu | Leu | Gly | Cys | Leu | Gly |
| | | | | 165 | | | | | 170 | | | | | 175 | |
| Ser | Glu | Thr | Arg | Arg | Leu | Ser | Leu | Phe | Leu | Val | Leu | Val | Val | Leu | Ser |
| | | | | 180 | | | | | 185 | | | | | 190 | |
| Ser | Leu | Gly | Glu | Met | Ala | Ile | Pro | Phe | Phe | Thr | Gly | Arg | Leu | Thr | Asp |
| | | | 195 | | | | | 200 | | | | | | 205 | |
| Trp | Ile | Leu | Gln | Asp | Gly | Ser | Ala | Asp | Thr | Phe | Thr | Arg | Asn | Leu | Thr |
| | | | 210 | | | | | 215 | | | | | | 220 | |
| Leu | Met | Ser | Ile | Leu | Thr | Ile | Ala | Ser | Ala | Val | Leu | Glu | Phe | Val | Gly |
| | | | 225 | | | | | 230 | | | | | | 235 | 240 |

Asp Gly Ile Tyr Asn Asn Thr Met Gly His Val His Ser His Leu Gln
245 250 255
Gly Glu Val Phe Gly Ala Val Leu Arg Gln Glu Thr Glu Phe Phe Gln
260 265 270
Gln Asn Gln Thr Gly Asn Ile Met Ser Arg Val Thr Glu Asp Thr Ser
275 280 285
Thr Leu Ser Asp Ser Leu Ser Glu Asn Leu Ser Leu Phe Leu Trp Tyr
290 295 300
Leu Val Arg Gly Leu Cys Leu Leu Gly Ile Met Leu Trp Gly Ser Val
305 310 315 320
Ser Leu Thr Met Val Thr Leu Ile Thr Leu Pro Leu Leu Phe Leu Leu
325 330 335
Pro Lys Lys Val Gly Lys Trp Tyr Gln Leu Leu Glu Val Gln Val Arg
340 345 350
Glu Ser Leu Ala Lys Ser Ser Gln Val Ala Ile Glu Ala Leu Ser Ala
355 360 365
Met Pro Thr Val Arg Ser Phe Ala Asn Glu Glu Gly Glu Ala Xaa Lys
370 375 380
Phe Arg Glu Lys Leu Gln Glu Ile Lys Thr Leu Asn Gln Lys Glu Ala
385 390 395 400
Val Ala Tyr Ala Val Asn Ser Trp Thr Thr Ser Ile Ser Gly Met Leu
405 410 415
Leu Lys Val Gly Ile Leu Tyr Ile Gly Gly Gln Leu Val Thr Ser Gly
420 425 430
Ala Val Ser Ser Gly Asn Leu Val Thr Phe Val Leu Tyr Gln Met Gln
435 440 445
Phe Thr Gln Ala Val Glu Val Leu Leu Ser Ile Tyr Pro Arg Val Gln
450 455 460
Lys Ala Val Gly Ser Ser Glu Lys Ile Phe Glu Tyr Leu Asp Arg Thr
465 470 475 480
Pro Arg Cys Pro Pro Ser Gly Leu Leu Thr Pro Leu His Leu Glu Gly
485 490 495
Leu Val Gln Phe Gln Asp Val Ser Phe Ala Tyr Pro Asn Arg Pro Asp
500 505 510

706

Val Leu Val Leu Gln Gly Leu Thr Phe Thr Leu Arg Pro Gly Glu Val
515 520 525

Thr Ala Leu Val Gly Pro Asn Gly Ser Gly Lys Ser Thr Val Ala Ala
530 535 540

Leu Leu Gln Asn Leu Tyr Gln Pro Thr Gly Gly Gln Leu Leu Leu Asp
545 550 555 560

Gly Lys Pro Leu Pro Gln Tyr Glu His Arg Tyr Leu His Arg Gln Val
565 570 575

Ala Ala Val Gly Gln Glu Pro Gln Val Phe Gly Arg Ser Leu Gln Glu
580 585 590

Asn Ile Ala Tyr Gly Leu Thr Gln Lys Pro Thr Met Glu Glu Ile Thr
595 600 605

Ala Ala Ala Val Lys Ser Gly Ala His Ser Phe Ile Ser Gly Leu Pro
610 615 620

Gln Gly Tyr Asp Thr Glu Val Asp Glu Ala Gly Ser Gln Leu Ser Gly
625 630 635 640

Gly Gln Arg Gln Ala Val Ala Leu Ala Arg Ala Leu Ile Arg Lys Pro
645 650 655

Cys Val Leu Ile Leu Asp Asp Ala Thr Ser Ala Leu Asp Ala Asn Ser
660 665 670

Gln Leu Gln Val Glu Gln Leu Leu Tyr Glu Ser Pro Glu Arg Tyr Xaa
675 680 685

Arg Xaa
690

<210> 727

<211> 82

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (44)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (73)

<223> Xaa equals any of the naturally occurring L-amino acids

<400> 727

Thr Pro Pro Leu Val Ser Ser Val Ala Ala Leu Asp Ser His Arg Ser
1 5 10 15

Thr Asn Pro Ile Val Asn Ser Ala Cys Lys Gly Ser Arg Leu Cys Ala
20 25 30

Pro Tyr Glu Asn Leu Met Pro Asp Asp Leu Arg Xaa Asn Ser Phe Ile
35 40 45

Leu Lys Pro Pro Phe Thr Leu Gln Ser Val Glu Lys Leu Ser Ser Thr
50 55 60

Lys Leu Val Pro Gly Ala Lys Asn Xaa Gly Asp Arg Cys Ser Arg Glu
65 70 75 80

Arg Ser

<210> 728

<211> 600

<212> PRT

<213> Homo sapiens

<220>

<221> SITE

<222> (11)

<223> Xaa equals any of the naturally occurring L-amino acids

<220>

<221> SITE

<222> (479)

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<220>

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<221> SITE

<222> (590)

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<400> 728

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Ser Arg Val Lys Pro Arg Val Arg Gly Thr Xaa Val Arg Thr Pro Gly
  1             5             10             15

Ser Arg Arg Gly Arg His Gly Ala Val Pro Gly Asp Trp Glu Ala Ala
      20             25             30

Ala Gln Ala Arg Gly Ala Gly Gln Arg Leu Pro Thr Pro Ser Glu Ile
      35             40             45

Leu Ser Asn Ala Gly Leu Arg Phe Glu Val Val Pro Ser Lys Phe Lys
      50             55             60

Glu Lys Leu Asp Lys Ala Ser Phe Ala Thr Pro Tyr Gly Tyr Ala Met
      65             70             75             80

Glu Thr Ala Lys Gln Lys Ala Leu Glu Val Ala Asn Arg Leu Tyr Gln
      85             90             95

Lys Asp Leu Arg Ala Pro Asp Val Val Ile Gly Ala Asp Thr Ile Val
      100            105            110

Thr Val Gly Gly Leu Ile Leu Glu Lys Pro Val Asp Lys Gln Asp Ala
      115            120            125

Tyr Arg Met Leu Ser Arg Leu Ser Gly Arg Glu His Ser Val Phe Thr
      130            135            140

Gly Val Ala Ile Val His Cys Ser Ser Lys Asp His Gln Leu Asp Thr
      145            150            155            160

Arg Val Ser Glu Phe Tyr Glu Glu Thr Lys Val Lys Phe Ser Glu Leu
      165            170            175

Ser Glu Glu Leu Leu Trp Glu Tyr Val His Ser Gly Glu Pro Met Asp
      180            185            190

Lys Ala Gly Gly Tyr Gly Ile Gln Ala Leu Gly Gly Met Leu Val Glu
      195            200            205

Ser Val His Gly Asp Phe Leu Asn Val Val Gly Phe Pro Leu Asn His
      210            215            220

Phe Cys Lys Gln Leu Val Lys Leu Tyr Tyr Pro Pro Arg Pro Glu Asp
      225            230            235            240

Leu Arg Arg Ser Val Lys His Asp Ser Ile Pro Ala Ala Asp Thr Phe
      245            250            255

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Glu Asp Leu Ser Asp Val Glu Gly Gly Gly Ser Glu Pro Thr Gln Arg
 260 265 270
 Asp Ala Gly Ser Arg Asp Glu Lys Ala Glu Ala Gly Glu Ala Gly Gln
 275 280 285
 Ala Thr Ala Glu Ala Glu Cys His Arg Thr Arg Glu Thr Leu Pro Pro
 290 295 300
 Phe Pro Thr Arg Leu Leu Glu Leu Ile Glu Gly Phe Met Leu Ser Lys
 305 310 315 320
 Gly Leu Leu Thr Ala Cys Lys Leu Lys Val Phe Asp Leu Leu Lys Asp
 325 330 335
 Glu Ala Pro Gln Lys Ala Ala Asp Ile Ala Ser Lys Val Asp Ala Ser
 340 345 350
 Ala Cys Gly Met Glu Arg Leu Leu Asp Ile Cys Ala Ala Met Gly Leu
 355 360 365
 Leu Glu Lys Thr Glu Gln Gly Tyr Ser Asn Thr Glu Thr Ala Asn Val
 370 375 380
 Tyr Leu Ala Ser Asp Gly Glu Tyr Ser Leu His Gly Phe Ile Met His
 385 390 395 400
 Asn Asn Asp Leu Thr Trp Asn Leu Phe Thr Tyr Leu Glu Phe Ala Ile
 405 410 415
 Arg Glu Gly Thr Asn Gln His His Arg Ala Leu Gly Lys Lys Ala Glu
 420 425 430
 Asp Leu Phe Gln Asp Ala Tyr Tyr Gln Ser Pro Glu Thr Arg Leu Arg
 435 440 445
 Phe Met Arg Ala Met His Gly Met Thr Lys Leu Thr Ala Cys Gln Val
 450 455 460
 Ala Thr Ala Phe Asn Leu Ser Arg Phe Ser Ser Ala Cys Asp Xaa Gly
 465 470 475 480
 Gly Cys Thr Gly Ala Leu Ala Arg Glu Leu Ala Arg Glu Tyr Pro Arg
 485 490 495
 Met Gln Val Thr Val Phe Asp Leu Pro Asp Ile Ile Glu Leu Ala Ala
 500 505 510
 His Phe Gln Pro Pro Gly Pro Gln Gln Cys Arg Ser Thr Ser Gln Gln
 515 520 525

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